

# The balance of power

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**Doctoral thesis**

**THE BALANCE OF POWER**

**INVESTIGATING ATTENTION NETWORK  
INTERACTIONS AND ALPHA POWER  
MODULATIONS USING NON-INVASIVE BRAIN  
STIMULATION**

Stefano Gallotto

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# **THE BALANCE OF POWER**

## **INVESTIGATING ATTENTION NETWORK INTERACTIONS AND ALPHA POWER MODULATIONS USING NON-INVASIVE BRAIN STIMULATION**

Dissertation

To obtain the degree of Doctor at Maastricht University,  
on the authority of the Rector Magnificus,  
Prof. Dr. Rianne M. Letschert,  
in accordance with the decision of the Board of Deans,  
to be defended in public on  
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# 1

## **Introduction**



A typical day starts with waking up, getting out of bed, and maybe having some breakfast. If you are fortunate enough to live in the Netherlands, you probably also jump on your bike to go to work. You arrive at work, and without even noticing it you went through many obstacles on the way, maybe while listening to music and thinking about what you will be presenting in the afternoon's meeting. At first this may sound simple and, maybe, not even that special. But if you stop for a second and think this through, you will probably realize how incredible, inexplicable and fascinating this actually is. In fact, even though these are simple daily life experiences, your brain has to process a large amount of information to accomplish seemingly effortless actions.

Neuroscience, in broad terms, focuses on the study of the nervous system including its anatomy, biology and physiology. Cognitive neuroscience, more specifically, aims to elucidate how from a physical organ such as the brain these experiences arise or, as one of the first and most influential neuroscientists – Michael Gazzaniga – said in simpler words, “how neurons generate mind” (Gazzaniga, 2018). As a multidisciplinary field, cognitive neuroscience represents a huge endeavor to understand the causality between cognition and the brain, and ultimately build conceptual models able to give insights into the organization and structure of brain functions.

A vast part of what we experience in our life comes from signals reaching the brain through five different avenues: sight, touch, hearing, smell, and taste. A specific system is then required to filter, select and organize the most relevant information, ultimately allowing the generation of coherent thoughts. Attention plays a major role in this process. In the visual modality it can be differentiated into three different types: spatial attention refers to shifting attention toward specific locations of the visual field, object-based attention refers to allocating attention to a specific object, and feature-based attention refers to focusing on certain characteristics of that object (e.g. motion direction, color) independently of its location in space (Carrasco, 2012; Olson & Chun, 2001; Scholl, 2001). Thus, by prioritizing different aspects, the brain is able to extract relevant information and organize it in a meaningful way.

The work presented in this thesis will (partly) focus on these conscious experiences in the visual domain, trying to relate them to oscillatory brain activity. An overview of the main studies that investigated the neural correlates of visual consciousness - the minimal set of neuronal mechanisms that are jointly sufficient for a conscious experience (Crick & Koch, 1990) - will be presented in Chapter 2. The following chapters will focus on two different aspects of visuospatial attention. One aspect relates the brain mechanisms underlying visuospatial attention to posterior alpha power oscillations, and their change after disruption of core nodes of the dorsal attention network. The other aspect moves one step forward in understanding how this brain network as a whole reacts after single and double disruption, trying in particular to unravel the interactions taking

place between its nodes. The present chapter provides a background for understanding the chapters that will follow, and motivates the importance of the work here presented both in terms of basic research as well as its benefits in the clinical context.

### 1.1 VISUOSPATIAL ATTENTION

In general terms, attention can be defined as the ability to focus on specific stimuli of our environment at the detriment of others. In the visual domain, this function is defined as visuospatial attention, and allows selecting and prioritizing specific portions of the visual field. This leads to an advantage for the information coming from those attended regions, since it is processed faster and more accurately than the others, which are inhibited instead (Posner & Petersen, 1990). Thus, orienting attention toward a relevant stimulus allows its correct identification and classification.

Such actions are usually accomplished by the synergistic work of different body systems, with attention playing a major role in their coordination. Overt attention refers to the simultaneous contribution of different systems to the improvement of stimulus processing. For example, when scanning a scene in front of us we focus on relevant stimuli by directing our attention toward them. At the same time, we also turn our head and move our trunk accordingly (Sokolov, 1963). Covert attention refers to focusing attention on a specific stimulus with only one system performing the action. For example, in the auditory domain this would mean directing attention toward the sound coming from outside your room without any other systems accompanying this action.

On a different level, the process of orienting attention toward relevant spatial locations can also be distinguished in exogenous attention and endogenous attention (Corbetta & Shulman, 2002). Exogenous attention responds in an automatic manner to salient and unexpected events. In fact, to deal with an environment that is constantly changing we need a flexible system that is able to rapidly adapt to new situations. For example, a car suddenly appearing from the right side of the bike lane might make you slow down without even realizing it. This is because its appearance grabbed your attention and instinctively made you react to it. In an ecological setting this mechanism helps to avoid possible threatening (and therefore relevant) situations by maximizing attentional resources that would otherwise not suffice to properly process the entire scene at once (Ferdinando et al., 2007). On the other hand, endogenous attention allows us to voluntarily direct our attention toward specific stimuli in our visual field, favoring their processing and leading to an advantage in terms of speed and accuracy (Posner, 1980). For example, looking at the river while crossing a bridge, you might notice a nice boat and decide to focus your attention on the flag

waving on its back to understand where it comes from. You are then able to focus your attention on the objects that are of interest despite the fact that the scene is surrounded by many other distracting stimuli. Thus, this function allows directing attention toward either a portion of visual space or selected stimuli, in order to enhance processing of information. Both types of attention work in synergy and allow goal-directed behavior as well as remaining vigilant in case of a sudden and potentially dangerous event (Corbetta et al., 2008; Corbetta & Shulman, 2002).

Exogenous attention and endogenous attention allow directing our focus in visual space, but are not the only mechanisms involved in this process. Let us suppose now you are waiting for the traffic light to turn green. A few seconds before this actually happens a cue alerts you that soon you will be able to go. In this moment there is an internal state change that allows you to get ready to depart. This example explains in a simple way the concept of alerting, which refers to the mechanisms a system puts in place when preparing to respond to an upcoming stimulus and maintaining a state of alertness. Intuitively, this mechanism leads to faster processing of information, since when an expected stimulus appears the system is already prepared to respond to it (Posner & Petersen, 1990; Posner & Rothbart, 2007). In an experimental setup this “readiness” is usually translated to faster reaction times and higher accuracy (Callejas et al., 2005).

If then the light takes longer than expected to turn green, you might need to inhibit this preparation in order to stop your departure and wait a few seconds more. In this case another type of mechanism intervenes. Executive control refers to the ability of monitoring and suppressing specific stimuli in order to select relevant information and resolve conflict among responses (Fan et al., 2003; Posner & Rothbart, 2007). Over the past decades, these three attention mechanisms (orienting, alerting, and executive control) have been extensively investigated, and many behavioral tasks have been developed in order to separate and study these aspects of attention individually.

A classic paradigm for studying attention orienting is the cueing task. Firstly developed by Posner (1980), this task prompts one’s attention to a specific part of their visual field by making use of symbolic cues. These cues are usually used to direct attention toward either the left or the right side of visual space, and precede the appearance of a target stimulus that needs to be detected. Participants sit in front a computer screen and maintain fixation on a central point. A symbolic (directional) cue is then briefly presented at the center of the screen, indicating to which side of the visual space attention should be deployed, as well as the probable location where the upcoming target will appear. Participants have to interpret the information provided by the cue and shift their attention accordingly. After a few hundred milliseconds a peripheral target appears either at the cued location, or at the opposite location, and their task is to identify as fast and accurately as possible some of its characteristic such as, for example, its

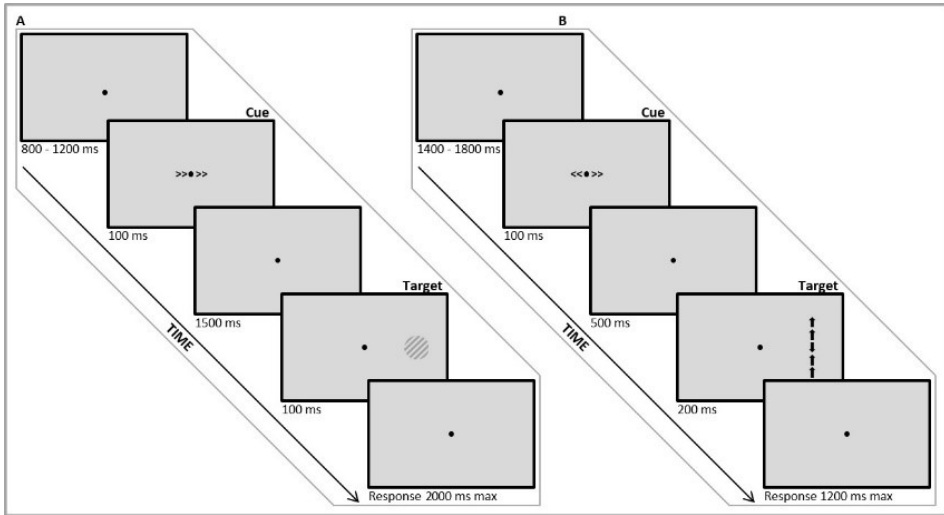


orientation. Faster reaction times and higher accuracy are usually observed when the visual information comes from attended locations (e.g. cue pointing toward the left, target appearing on the left side of the central point) as compared to unattended locations (e.g. cue pointing toward the right, target appearing on the left side of the central point). In our implementation of the task we also included a “neutral” cue condition. In this case the cue points toward both directions (left and right), exposing participants to the same amount of visual information as the directional cue conditions, but without providing them any spatial information regarding the location of the upcoming target stimulus.

The combination of cue condition (left, right, and neutral) and target location (left, right) generates six different conditions, which are commonly defined as valid when cue direction and target location are coherent, invalid when targets appear on the opposite location from what the cue suggested, and neutral in case of a neutral cue, either for the left or right hemifield. If participants correctly follow the spatial information provided by the cue, attention performances are typically faster for valid trials and slower for invalid trials, both compared to neutral trials. The difference in reaction times observed between valid and neutral trials quantifies the advantage of allocating attentional resources already on the right location, where the target actually appears (attentional benefit). The difference in reaction times between neutral trials and invalid trials quantifies the disadvantage of having to reallocate attention toward the correct target location, after it was allocated elsewhere (attentional cost). Moreover, it is important to stress that, in order for the task to generate the intended effects, participants have to follow the instruction provided by the cues. Thus, valid cues are usually presented more often than invalid cues (approximately 80% of the directional cues), so that participants “trust” the information they provide and shift their attention accordingly.

In one of the experiments presented in this thesis not only did we investigate orienting mechanisms, but also alerting and executive control mechanisms. A task that is able to capture all these facets of attention was conceived by Posner and Raichle (1994), the so-called attention network test (ANT). Other than the directional and neutral cue conditions previously described, this task comprises also a no cue condition which does not provide spatial nor temporal information. Since the neutral cue condition announces the appearance of the upcoming event preparing for its identification, its comparison with the no cue condition allows isolating alerting effects. Lastly, distractors (i.e. flankers) presented next to target stimuli allow investigating executive control mechanisms. This is because they interfere with the identification of the targets and therefore need to be inhibited (Eriksen & Eriksen, 1974).

The ANT measures the efficiency of orienting, alerting, and executive control processes independently and in a reliable way (Fan et al., 2001, 2002). A more recent version of this task (the lateralized-ANT, LANT) allows investigating these three attention components separately in the left hemifield and in the right hemifield. Emphasizing differences between hemifields is crucial when the function under investigation is known to be characterized by a certain functional asymmetry in the brain, with one hemisphere being more prevalent than the other hemisphere. Fig. 1 shows examples of both the “classic” Posner task and the LANT used in our experiments.



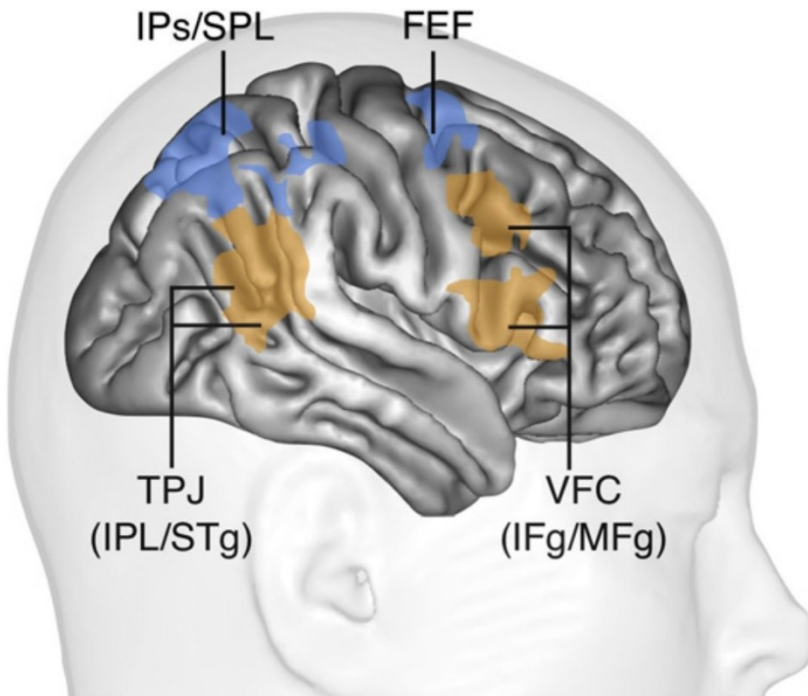
**Figure 1:** Representations of possible trials and time intervals between trial events. A) A typical attention task example: a cue prompts attention toward the right hemifield and the target (Gabor patch) appears at the same location (valid trial). B) LANT example: a cue prompts attention toward both left and the right hemifields (neutral trial) and an incongruent target appears.

## 1.2 BRAIN NETWORKS OF ATTENTION

Attentional processes are supported by the synergistic work of several regions in the brain that together form different functional networks. In this context, one of the most influential models has been proposed by Corbetta & Shulman (2011). Their functional-anatomical model suggests two separate but highly interacting networks as responsible for spatial attentional control. As previously mentioned, orienting of attention comprises exogenous and endogenous attention. Exogenous attention intervenes when unexpected but behaviorally relevant stimuli appear in our environment. This bottom-up attentional process is (mostly) ascribed to a

ventral attention network (VAN), which is right-lateralized and composed of temporoparietal junction (anatomically defined as the intersection of superior temporal gyrus, inferior parietal lobule, and lateral occipital cortex) and ventral frontal cortex. The VAN interrupts the voluntary deployment of attention, allowing its reallocation in case a relevant stimulus suddenly appears. Endogenous attention is implicated when shifting attention in visual space in a voluntary manner. This top-down attentional control is supported by the so-called dorsal attention network (DAN), which is mainly constituted by the frontal eye field (FEF) in frontal cortex, and the intraparietal sulcus (IPS) in parietal cortex (Corbetta & Shulman, 2002, 2011; Mesulam, 1999). Together, these two regions allow shifting attention in visual space. Several studies have shown that signals originate in the FEF and are sent back toward parietal cortex via top-down influences. IPS then exerts control over the occipital cortex (Kastner & Ungerleider, 2000; Reynolds & Chelazzi, 2004) which eventually coordinates and modulates stimulus processing. Thus, the interaction between these two core DAN nodes eventually allows achieving enhanced processing in a specific part of the visual field (Moore & Fallah, 2004; Noudoost et al., 2010) or of a specific stimulus (Carrasco et al., 2004) by selectively recruiting the neurons responsible for the properties of that stimulus (McAdams & Maunsell, 1999; Reynolds, J. H. et al., 2000). When multiple stimuli are presented at the same time, attention can resolve the competition that naturally emerges between them by increasing the neuronal response of the attended stimulus, thus prioritizing its processing over the other stimuli (Reynolds et al., 1999).

A wealth of empirical studies has shown the relevance of the DAN for attention processes both in healthy participants and clinical population. Functional magnetic resonance imaging (fMRI) studies demonstrated modulation of brain activity in the DAN network during shifts of attention (Corbetta et al., 2000; Hopfinger et al., 2000; Kastner et al., 1999), and a correlation between how strongly its nodes are interconnected and behavioral performance has been observed (Szczepanski et al., 2013).



**Figure 2:** The two fronto-parietal networks classically defined as responsible for endogenous and exogenous attention. The dorsal attentional network (composed of frontal eye field, FEF; intraparietal sulcus, IPS; and superior parietal lobe, SPL) is represented in blue. The ventral attention network (composed of ventral frontal cortex, VFC; and temporoparietal junction, TPJ) is represented in yellow. This functional-anatomical model was proposed by Corbetta and Shulman (2002). The figure is adapted from Chica, Bartolomeo and Lupiáñez (2012).

Alerting mechanisms have been shown to activate fronto-parietal cortical regions as well as thalamic regions (Fan, Flombaum, McCandliss, Thomas, & Posner, 2003). This evidence has also been supported by clinical and behavioral data, demonstrating that these activations are mostly prominent in the right hemisphere (Posner & Petersen, 1990; Sturm et al., 1999, 2006; Sturm & Willmes, 2001) as it has often been observed with attentional processes. Specifically, these activations have been observed in superior parietal lobule, middle and superior frontal gyri, anterior cingulate cortex, and thalamus (Fan et al., 2007). Regarding executive control mechanisms, a network comprising anterior cingulate cortex, prefrontal and orbitofrontal cortices, supplementary motor area, basal ganglia (in part), and the thalamus, has been shown to be active

in tasks involving inhibition and conflict resolution (Bush et al., 2000; Carter et al., 1999; Fernandez-Duque & Posner, 2001; Posner & Rothbart, 1998).

## 1.3 VISUOSPATIAL ATTENTION THEORIES

The studies previously reported showed evidence that different brain networks are responsible for different attentional processes. The role of these networks, though, is still under investigation, and further research will be necessary in order to (hopefully) elucidate it. This becomes evident if we think that even ascribing specific hemispheric involvements for attention processes is still matter of debate, though over the years several theories tried to correctly explain and predict brain functioning related to them. These theories mostly emerged from the observation of visuo-spatial hemineglect, whose symptoms often occur after unilateral hemispheric damage (usually stroke) to fronto-parietal or sub-cortical brain regions. Patients suffering from this neuropsychological syndrome are typically unable to attend and report stimuli presented on the contralesional side of visual space, even though visual perception is preserved and appears to be intact. This inability is the consequence of a strong spatial attention bias toward the ipsilesional side of visual space, and is more commonly observed after right hemispheric damage. This observation suggests a functional asymmetry underlying spatial attention consistent with a right hemispheric dominance (Mesulam, 1981). Moreover, this syndrome also includes disorders of awareness, with patients often neglecting their illness and the obvious deficits that characterize it (Corbetta & Shulman, 2011).

Starting from these symptoms, and the fact that they appear more often after damage of the right hemisphere (Corbetta et al., 2005), two theories became quite prominent over the last few decades, trying to relate the contribution of each hemisphere to visuospatial attention.

The *hemispatial* theory of attention postulates that both hemispheres are involved when shifting attention toward the contralateral side of visual space, but only the right hemisphere also when shifting attention toward the ipsilateral side of visual space (Heilman & Van Den Abell, 1980). From a clinical point of view, hemineglect symptoms mostly appearing in the left hemispace would then be a consequence of a right hemispheric damage leading to deficits in the processing of contralateral stimuli, and the left hemisphere being unable to compensate for this dysfunction. In case of left hemispheric damage these deficits would not be as evident simply because the right hemisphere is still be able to account for both sides of visual space. Thus, this theory proposes a functional asymmetry favoring a right hemispheric dominance.

As a direct competitor, the *interhemispheric competition* theory of attention states that both hemispheres compete in attention, each of them exerting

a bias toward the contralateral side of visual space, with the left hemisphere exerting a stronger bias compared to the right hemisphere. A balance in attention is eventually reached via transcallosal inhibition (Kinsbourne, 1977). In this case, hemineglect symptoms would emerge more often after right hemispheric damage due to a hugely unbalanced mutual inhibition, with the stronger rightward bias generated by the left hemisphere left unopposed and the focus of attention completely shifted toward the right hemifield. Left hemispheric damage would not cause such severe symptoms because the bias generated by the right hemisphere is not as strong as the bias generated by the left hemisphere. Thus, even if the right hemisphere is left unopposed, it is not able to move the shift of attention toward the utmost left side of visual space, showing symptoms that are not as severe as the ones observed after right hemispheric damage. This theory supports the notion of left hemispheric dominance in attention.

Recent developments tried to integrate insights from both clinical and brain stimulation studies and proposed a functional-anatomical model that combines both theories, but separates them based on brain anatomy (Duecker & Sack, 2015). The model suggests that the hemispacial theory of attention applies to frontal regions, with the right FEF being able to direct attention toward both left and right hemifields, and the left FEF only toward the contralateral hemifield. Parietal regions would be more in line with the interhemispheric theory of attention, being involved when attention is shifted toward the contralateral side of visual space, and characterized by hemispheric competition. Thus, the functional asymmetry usually assumed in attention would be region-specific, with frontal regions showing right hemispheric dominance, and posterior regions showing left hemispheric dominance. Clinical symptoms would be independent of whether brain damage occurred in frontal or parietal regions of the right hemisphere, since in both cases deficits would be confined to the left hemifield. What is important to clarify, though, is that the underlying mechanisms would be completely different, given the different roles these regions would play in attention.

These different models try to explain the correct functioning of the healthy brain and how attention can be impaired after brain damage. Intuitively, these theories are inherently related to the anatomical brain networks previously mentioned. Given the complexity of these networks, it appears immediately clear that the mechanisms taking place within and across them are difficult to disentangle, with their interactions becoming even more difficult to predict after brain damage. Thus, it is of paramount importance to have models that are able to reliably predict such mechanisms.

To date, this fine-grained knowledge is still missing, and it is only by using a multimodal approach and tackling the problem from different angles that such challenges can be solved. Such a multimodal approach ideally uses a combination of non-invasive brain modulation and brain imaging techniques to study the

behaviorally controlled execution of visuospatial attention in healthy volunteers. In this context, the assessment of attention-related changes in the temporal structure of neural activity within specific brain networks assessed by electroencephalography (EEG) has been crucial to start unravelling this mysterious relationship between brain and attention, and it also plays a key role in the current dissertation.

## 1.4 ELECTROENCEPHALOGRAPHY

One of the most important aspects we can investigate in the context of attention is oscillatory brain activity. As will be explained below, oscillations are crucially involved in attentional processes, elucidating and giving important insights into their nature. In this section, the methodology that is able to capture these electrophysiological signals will be introduced.

Oscillatory brain activity can be recorded from the scalp by means of electrodes that pick up electrical signals generated in the brain. These signals reflect synchronous firing of (mostly) pyramidal neurons that are perpendicular to the cortical surface. Neurotransmitters are released into the synaptic cleft and bind to receptors of the postsynaptic neuron, causing the soma to depolarize. When excitatory and inhibitory postsynaptic dendritic currents are generated in neurons placed in a columnar alignment and that fire together in a certain rhythmicity, an oscillatory activity pattern emerges (Creutzfeldt et al., 1966; Proudfoot et al., 2014).

Electroencephalography (EEG) is able to detect this activity and transform it into signals that convey meaningful information about brain functioning. One of the main advantages of EEG is to have a very high temporal resolution, allowing the study of brain function in the order of milliseconds. Oscillating signals are characterized by three parameters: frequency, amplitude, and phase. The frequency relates to how often the activity cycle goes up and down in a certain unit of time (generally one second) and is measured in Hertz (Hz). Oscillatory brain activity can roughly be distinguished in five different frequency bands: delta (< 4 Hz), theta (4-6 Hz), alpha (7-13 Hz), beta (14-30 Hz), gamma (> 30 Hz). It has been shown that different networks in the brain and their associated cognitive processes are naturally characterized by different frequencies (Keitel and Gross, 2016). For instance, occipital and parietal brain areas are mostly characterized by alpha activity, and sensory areas by alpha as well as beta activities (Hari & Salmelin, 1997; Hillebrand et al., 2012; Pfurtscheller et al., 1996). The amplitude (power) reflects in general terms the strength of an oscillatory activity, directly relating to how much an oscillation with a certain frequency is present in the signal. This ultimately translates to how many (and to what extent) pyramidal cells fire in a synchronized manner in a

particular frequency. Lastly, the cyclic pattern of activity that is observed at the population level reflects high and low levels of activity. Where the signal is at a certain moment in time along this sinusoidal pattern represents its phase. This appears to be relevant, for example, when investigating the relation between behavioral performance and phase similarity at target presentation across repeated trials (i.e. phase-locking; Tallon-Baudry et al., 1996).

Since brain regions interact forming functional networks, evaluating phase-locking between core nodes of a given brain network – how consistent the phase relationship is between two oscillating signals when a particular event occurs – can give insights into the brain mechanisms underlying the brain function such a network supports. Specifically, this would be defined as phase coherence (Srinivasan et al., 1999). Signals originating from two nodes of the same brain network oscillating with same phase suggest functional connectivity between these regions.

Data obtained with EEG measurements reflect a combination of signal power and noise power – the so-called signal-to-noise ratio (SNR). To increase the SNR, EEG experiments generally comprise many trials repeated over time, with the experimental conditions kept as similar as possible but for the cognitive process of interest. This is based on the assumption that by averaging the same condition across multiple trials the noise power cancels itself out, only leaving the oscillatory activity related to the function that is being studied.

Brain functions are modulated over time, being in one moment more active than in other moments. Since oscillatory signals reflect this constantly changing activity, they do change over time accordingly. Thus, analyzing oscillatory brain activity over time instead of performing stationary frequency analyses can give much richer and more meaningful insights into the brain mechanisms underlying a certain brain function, how it modulates, and how it adapts.

## 1.5 ALPHA OSCILLATIONS

As mentioned above, the attention mechanisms that take place within the DAN when attention is deployed in visual space ultimately lead to the modulation of brain activity in sensory areas that process the incoming visual information. It has been demonstrated that this mechanism operates via oscillatory mechanisms (i.e. brain oscillations), which govern enhancement or inhibition of neuronal activity in those regions (Engel & Singer, 2001; Jensen & Mazaheri, 2010).

The alpha rhythm (7-13 Hz) is one of the most evident signals in the EEG trace, becoming prominent especially in occipito-parietal sites when the eyes are closed (Berger, 1929). This has made early electrophysiologists think that it mostly reflects a relaxed state. When a brain region becomes inactive, for example due to absence of visual information as after closing the eyes, these alpha



oscillatory patterns emerge (Pfurtscheller et al., 1996). Thus, this mechanism would reflect an automatic transition from an active state to an inactive state. More recent views believe that alpha activity is the electrophysiological marker of an “active inhibition”, namely that this state is actively produced rather than being a consequence of an absence of information (Klimesch et al., 2007).

When attention is voluntarily shifted toward one hemifield, alpha activity in parieto-occipital areas gets modulated showing lateralization. To estimate this modulation, most studies computed the relative change in terms of alpha power between left and right hemispheres and/or hemifields. If indeed there is a hemisphere-specific change in the alpha activity during this process, then this computation should either lead to positive or negative values. An assumption that is commonly made is that, depending on where attention is allocated, alpha oscillations increase in the ipsilateral hemisphere and decrease in the contralateral hemisphere (Gould et al., 2011; Händel et al., 2011; Kelly et al., 2006; Rihs et al., 2007, 2009; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000; Yamagishi et al., 2003, 2005). Moreover, this lateralization has been even shown to reflect spatially-specific attentional biases spontaneously occurring in visual tasks (Boncompagni et al., 2016). From a cognitive point of view, this mechanism appears to be quite interesting, since it can be reliably linked to attention processes, thus allowing their investigation. In experimental settings, alpha activity has been studied by employing tasks that explicitly require participants to shift attention in a voluntary manner (Dombrowe & Hilgetag, 2014; Rihs et al., 2007; Sauseng et al., 2005; Worden et al., 2000; Yamagishi et al., 2005) or that implicitly link its modulation to variations in perceptual performance (Hanslmayr et al., 2007; Lange et al., 2013; van Dijk et al., 2008). Furthermore, alpha power changes prior to the presentation of expected targets can be predictive of general task performance (Händel et al., 2011; Hanslmayr et al., 2007; Thut et al., 2006; van Dijk et al., 2008).

One problem related to the methods mentioned above is that they do not allow separating single hemispheric contributions in terms of alpha activity to left and right shifts of attention. This is because lateralization scores are usually computed by collapsing alpha activity across left and right attention shifts in the same hemisphere, or across hemispheres within the same hemifield. Thus, the individual hemispheric contribution to the attentional control remains puzzling. By exploiting the tight relation between attention deployment and alpha power modulation in combination with a novel experimental task, we overcame this problem and revealed the single-hemispheric involvement to this process. And yet, in order to really test the causal relevance of certain brain areas and networks, or certain spatiotemporal coding principles underlying attention, one needs not only to assess neural activity changes during the behaviorally-controlled execution of different attention tasks, but ideally also to use techniques that allow stimulating and modulating these neural activity patterns non-invasively,

bringing them under experimental control. One of the most versatile non-invasive brain stimulation techniques is transcranial magnetic stimulation (TMS). This technique has been widely used in the experiments presented in the empirical chapters of this thesis, and will therefore be shortly introduced in the following section.

## 1.6 TRANSCRANIAL MAGNETIC STIMULATION

Non-invasive brain stimulation techniques have a crucial role in the study of the human brain. This is because having information about temporo-spatial brain activity patterns, such as the one obtained when employing neuroimaging techniques, only shows their correlation with specific brain functions/regions, but does not imply causality. To move beyond correlation, it is necessary to employ techniques that allow interacting with the brain activity itself. This would allow understanding whether specific brain regions/networks are responsible for given brain functions, thus showing their functional relevance and demonstrating causation.

By generating a magnetic field, transcranial magnetic stimulation (TMS) is able to painlessly interact with the cortex and transiently modulate brain activity (Hallett, 2000; Pascual-Leone et al., 2000; Sack, 2006; Walsh & Cowey, 2000). The TMS device is composed of two main elements: a stimulator and a TMS coil. The stimulator is able to generate a strong electric current. When it is discharged, the current goes through a cable and reaches the coil where a magnetic field is briefly generated (pulse). When the coil is positioned tangentially to the head and a pulse is delivered, the magnetic field perpendicularly passes through the skull and reaches the brain tissue underneath. This rapid change in magnetic field induces an electric field in the stimulated region that interacts with the normal neuronal transmission between neurons, which by nature involves electric signal exchanges. Stimulation effects reach (mainly) the cortex but are not able to go deeper and (directly) induce effects on sub-cortical regions. Different TMS parameters determine path and strength of stimulation and, as a direct consequence, the type of activity change induced in the brain. These parameters include the type of coil and its position/orientation during TMS application, the intensity (strength) of the pulses, and at which frequency they are delivered.

The type of coil that is used (partly) determines depth and focality of the magnetic field. One of the most commonly used types of coil consists of two copper wires placed next to each other in such a way that a figure-of-eight configuration is created. This arrangement allows the magnetic field to be strongest exactly where the two wires overlap and generates a very focal magnetic field, being able to stimulate small brain regions. Having high focality also

requires the TMS coil to be precisely positioned over the region of interest and its angle with respect to the orientation of the axons needs to be carefully adjusted. Since even a small change in one of these parameters might result in missing the area that is under investigation, to best achieve a positive result it is recommended to combine TMS with sophisticated coil positioning approaches such as neuronavigation. This combination allows assuring that the coil is correctly positioned, with the magnetic field reaching the region of interest and successfully inducing the desired effect.

The strength of stimulation is determined before the actual TMS application and is based on the resting motor threshold (rMT). Participants are asked to have their contralateral hand (with respect to the site of stimulation) at rest while the experimenter delivers single pulses over the motor cortex. The minimum intensity that is able to induce a movement of the contralateral abductor pollicis brevis in 50% of the pulses (e.g. in 5 out of 10 pulses) is used as a motor threshold (Rossini et al., 1994).

Lastly, depending on the frequency of stimulation a different change in cortical excitability is induced. As a rule-of-thumb, protocols employing low frequencies inhibit brain activity (Pascual-Leone et al., 2000), whereas protocols employing high frequencies increase brain activity (Hilgetag et al., 2001), respectively leading to reduced or enhanced information processing, with a temporal effect that can vary from milliseconds to minutes. In our studies we used the continuous theta burst stimulation (cTBS) protocol, which is capable of inhibiting brain activity. This protocol consists of 600 pulses delivered in triplets five times per second with a stimulation intensity set to 80% of the rMT, leading to a stimulation of 40 seconds that induces long-lasting effects for about one hour (Huang et al., 2005). This allows applying TMS offline (i.e. before performing the task), thus avoiding effects that are not directly related to brain activity changes but still interfere with the task. These effects include muscle twitching, blinking, the sound generated by the pulse. Thus, offline protocols have clear advantages that online protocols (i.e. applied while performing the task) cannot have.

Using inhibitory protocols usually leads to a decreased efficiency of the targeted region, and when applied in the context of attention has functional consequences mimicking the ones observed after brain damage (Sack, 2010). The ability to disrupt brain activity only for a certain period of time allows using these protocols to causally study specific brain regions and the functions they are responsible for. If the stimulation was successful in targeting the region of interest, and such a region was indeed implicated in the brain function under investigation, TMS inhibition is then eventually converted in observable task performance/brain activity changes. Concretely, these consequences are not as evident as the ones occurring after brain damage, but in fact only translate into

small and reversible effects such as, for example, slower reaction time and/or lower accuracy.

TMS has been extensively employed to study the functional role of core nodes of the DAN network both in terms of behavioral changes using attention tasks and brain activity modulation using neuroimaging techniques (Duecker et al., 2013; Ruff et al., 2009; Sack et al., 2005, 2002, 2007; Thut et al., 2005). It has been shown that inhibitory TMS protocols applied to left or right FEF affect performance in tasks requiring endogenous shifts of attention (Duecker et al., 2013; Grosbras & Paus, 2002; Marshall et al., 2015). The parietal node of the DAN network has been even more often investigated, similarly showing an effect on attention performance using visuospatial attention tasks (Battelli et al., 2008; Bien et al., 2012; Dambeck et al., 2006; Hilgetag et al., 2001; Sack et al., 2002; Thut et al., 2005).

Furthermore, not only TMS has been shown to be quite useful for establishing the role of core nodes of the DAN network, but also all the related processes that happen in downstream areas, and that are as well affected by the stimulation. For example, by assessing cortical excitability in extrastriate cortex, Silvanto et al. (2006) have shown the central role FEFs have in mediating top-down influences. Likewise, the mechanisms mentioned above through which the DAN network exerts control over sensory areas (i.e. oscillations), have also been shown to be altered after FEF stimulation. Investigating them with TMS can actually be quite informative, revealing fine-grained neural mechanisms underlying attentional processes (Marshall et al., 2015; Ruff et al., 2006; Taylor et al., 2007).

Interestingly, this technique allows also studying how brain networks react when multiple nodes are stimulated, thus investigating neurophysiological mechanisms at local level (within the targeted regions), as well as at network level. In fact, possible compensatory mechanisms might be employed to counteract the disruption effects induced by TMS application, rebalance the activity of the network to the baseline level present before stimulation (Hartwigsen, 2018), and maintain behavior functional (Bortoletto et al., 2015; Eldaief et al., 2011; Hampson, 2010; Sack et al., 2005, 2007). For example, behavioral effects following stimulation of a single node may be unmasked only when applying a sequential TMS disruption approach to block the compensatory response of a second node (Sack et al., 2005).

Most of the TMS studies investigating attention, though, have used single-node stimulation rather than simultaneously modulating multiple nodes of a given network. Thus, the exact dynamics and interactions happening within the DAN network after stimulation remain elusive. How would a brain network react if multiple nodes were inhibited? Having this information appears to be fundamental to draw strong conclusions about the functional role core nodes of the network have. To address this question, in one of the studies reported in this

thesis we applied a cTBS protocol to single nodes of the DAN network as well as to two nodes sequentially, inducing concurrent inhibition of both nodes.

## 1.7 OUTLINE OF THE THESIS

This thesis represents an endeavor to achieve a comprehensive understanding of the functionality of the DAN network. We employed different brain techniques such as fMRI, TMS and EEG to reveal the exact dynamics within specific brain networks when attention is deployed in visual space. The obtained knowledge has crucial implications for both understanding the mechanisms underlying visuospatial attention in the healthy brain and the improvement of clinical applications in attention deficits after brain injury or disease. The experiments presented in this thesis make direct contributions by addressing the following research questions: 1) what is the role of oscillatory mechanisms in the visual domain? 2) How is alpha activity modulated in each hemisphere when visuospatial attention is deployed toward the left and the right hemifield? This directly relates to what role each hemisphere holds when shifting attention in visual space. 3) How are left and right FEFs (core nodes of the DAN network) causally involved in this process? 4) Do TMS effects on posterior alpha modulation change within the cue-target interval? If so, when are they most effective? 5) Is stimulating multiple nodes of a given network more effective than the more conventional single-node stimulation, and can it reveal meaningful insights into the interactions taking place within the network?

In the following chapters we first introduce the concept of oscillations, explaining what their pivotal role in visual conscious experiences is and describing why they are crucial for understanding basic brain functions. This first part presented in **Chapter 2** helps to introduce the EEG methodology that will be used in the subsequent experiments. In **Chapter 3** the concept of visuospatial attention is introduced. In this experiment we derived specific predictions from two leading theories of visuospatial attention, namely the ‘hemispatial’ theory of attention proposed by Heilman & Van Den Abell (1980) and the ‘interhemispheric competition’ theory of attention proposed by Kinsbourne (1977). By combining EEG with an innovative behavioral task, in this experiment we were able to test these predictions and reveal brain mechanisms related to this process hitherto unknown. We included a neutral cue condition used as a baseline, and dissociated leftward and rightward shifts of attention. We then related the obtained hemisphere-specific alpha power modulations to the predictions generated by the above-mentioned visuospatial attention theories, and dissociated different aspects of attention based on the brain activity patterns observed. This experiment showed that these two theories are not mutually exclusive but rather apply to different attentional states. In the study reported in **Chapter 4** the

network responsible for deploying attention in visual space is investigated by means of fMRI, TMS and EEG. fMRI-guided TMS has been employed to disrupt either left or right FEF individually. Effects of this disruption have then been assessed both behaviorally and using EEG measurements. The EEG analyses focused on understanding how FEF inhibition affected top-down influences and the related posterior alpha power modulations. Again, we also here used our novel approach to distill single hemispheric activations related to left and right attention shifts and assess how these were altered by FEF disruption. In the study reported in **Chapter 5** TMS has been employed to investigate the neurophysiological mechanisms employed by the DAN network when single and multiple nodes are targeted with inhibitory TMS. The aim of the experiment was to understand the interactions happening between core nodes of the DAN network after stimulation, and possibly improve therapeutic TMS applications. We demonstrated the great potential multi-site stimulation might have for both basic research and clinical applications, in order to have superior and more robust effects.

These experiments allowed us to contribute to unravelling (some of) the fine-grained mechanisms underlying visuospatial attention, and to gain a better understanding of the neural interactions happening between nodes of the DAN network. A future challenge will be to integrate this knowledge and translate it into applications that are able to enhance brain activity. This would allow having a greater outcome when restoring the loss of brain function.

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# 2

## Oscillatory correlates of visual consciousness

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## ABSTRACT

Conscious experiences are linked to activity in our brain: the neural correlates of consciousness (NCC). Empirical research on these NCCs covers a wide range of brain activity signals, measures, and methodologies. In this paper we focus on spontaneous brain oscillations; rhythmic fluctuations of neuronal (population) activity which can be characterized by a range of parameters, such as frequency, amplitude (power), and phase. We provide an overview of oscillatory measures that appear to correlate with conscious perception. We also discuss how increasingly sophisticated techniques allow us to study the causal role of oscillatory activity in conscious perception (i.e. ‘entrainment’). This review of *oscillatory correlates of consciousness* suggests that, for example, activity in the alpha-band (7-13 Hz) may index, or even causally support, conscious perception. But such results also showcase an increasingly acknowledged difficulty in NCC research; the challenge of separating neural activity necessary for conscious experience to arise (prerequisites) from neural activity underlying the conscious experience itself (substrates) or its results (consequences).

## 2.1 INTRODUCTION

In the last few decades, progress in technology and signal analysis have resulted in new neuroimaging and electrophysiology techniques, greatly enhancing the range and resolution of brain research applications. As such, our understanding of the brain has proceeded at a staggering pace. Naturally, these techniques have been tried on the oldest problem of all: the nature of consciousness.

‘Consciousness’ can be defined in many ways (for our own taxonomy, see de Graaf & Sack, 2014; de Graaf, Hsieh, & Sack, 2012). Generally, it is useful to separate minimally two concepts of consciousness. ‘State consciousness’ determines consciousness on a global level, for example distinguishing the extent of consciousness in coma, wakefulness, or anesthesia (e.g. Koch, 2004; Laureys & Tononi 2010). ‘Content consciousness’ refers to moment-by-moment experiences of a conscious being, such as the experience of seeing blue, hearing a trumpet, or the famous ‘what-it-is-like’ to momentarily be a bat (Nagel, 1974). In this article, we focus on content consciousness, specifically in the visual modality.

The neural correlates of consciousness (NCCs) have been defined as the minimal set of neuronal mechanisms that are jointly sufficient for a conscious experience (Crick & Koch, 1990b).

To study NCCs, one generally tries to induce minimally two different

conscious experiences using ‘consciousness paradigms’ (e.g. illusions, multistable and ON-OFF paradigms (de Graaf & Sack, 2014; Kim & Blake, 2005)), to then measure and compare brain activity in both (with neuroimaging techniques). This basic approach has been referred to as ‘contrastive analysis’ (Aru, Bachmann, Singer, & Melloni, 2012b; Baars, 1989). It can help reveal endogenous neural mechanisms underlying conscious perception, particularly if the physical stimuli remain identical in both conscious states. For example, when a low-intensity visual stimulus is repeatedly presented at perception threshold, the participant consciously perceives it on some but not on all trials. Thus, under identical stimulation conditions, this creates two types of trials: trials with conscious perception (ON) and trials without conscious perception (OFF) (de Graaf & Sack, 2014).

Different neuroimaging techniques can compare brain activity in both types of trials, such as functional magnetic resonance imaging (fMRI), magneto-/electroencephalography (M/EEG), electrocorticography (ECoG), or positron emission tomography (PET). Each has distinct advantages and applications, but here we focus on M/EEG, which can detect rhythmic fluctuations of brain activity, i.e. oscillations, with high temporal resolution. This is valuable as there is increasing evidence that oscillatory signatures may index conscious perception (e.g. Busch, Dubois, & VanRullen, 2009; Hanslmayr, Aslan, Staudigl, Klimesch, Herrmann, & Bäuml, 2007; Lange, Oostenveld, & Fries, 2013; Romei, Rihs, Brodbeck, & Thut, 2008b). We here review such evidence, organized by frequency-band. For some of the oscillatory correlates of consciousness, recent studies investigated their causal contribution to conscious perception. By using brain stimulation techniques or rhythmic sensory stimulation, fascinating new ‘entrainment’ approaches allow the experimenter to control oscillatory activity to evaluate its causal role in conscious perception. From this overview, we address the question; what are the oscillatory correlates of consciousness?

In addressing this question, this review has three goals. Firstly, it is meant to be instructive. We provide a basic overview of oscillations and how to measure them, paradigms used to identify, isolate, and study consciousness, and results: oscillatory measures reported to correlate with (visual) consciousness using such approaches. Secondly, we draw attention to the recent applications of entrainment to study the causal role of these oscillatory measures. Thirdly, we use the reviewed findings to illuminate an old problem: how to determine the functional role of such mechanisms? We have previously discussed how NCC, of any type or form, can factually be three sorts of processes: neural prerequisites, neural substrates, and neural consequences of a conscious experience (de Graaf et al., 2012; de Graaf & Sack, 2014). Interpreting oscillatory correlates of consciousness in this framework may provide new insights, and should be kept in mind when designing and interpreting future studies.

## 2.2 HOW TO STUDY OSCILLATORY CORRELATES OF CONSCIOUSNESS?

### 2.2.1 Consciousness paradigms

Generally speaking, consciousness paradigms share the ability to induce at least two different conscious percepts of a physically identical stimulus (Blake & Logothetis, 2002; Logothetis, 1998). We previously grouped them into three different categories: illusions, multistable paradigms, and ON-OFF paradigms (de Graaf & Sack, 2014; 2015), illustrated in Figure 1.

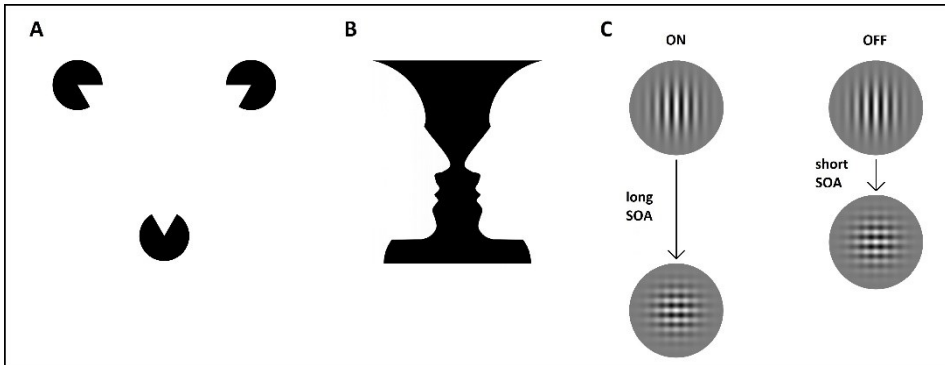
*Illusions* are conscious percepts that are created endogenously, in absence of sensory information from the physical environment usually causing the conscious percept now observed (i.e., in other situations or in other observers). A famous example is the Kanizsa triangle (Kanizsa, 1976): one perceives triangle-contours, even though lines delineating the sides of the triangle – which usually cause the conscious triangle percept – are missing from the image. Illusions can be useful to study consciousness, since brain activity correlated to their perception reflects ‘constructive’ processes of conscious vision (Goebel et al., 1998). A different approach involves afterimages: a percept remains present in visual experience even though the stimulus that evoked it has been removed (Zaidi et al., 2012). Hallucinations, lastly, do not involve any input and might be classified as illusions as well. They are typically present in pathologies as schizophrenia, in which the patient can experience different percepts (e.g., auditory, olfactory) in the total absence of external stimulation. But in fact, many of us may perceive hallucinatory illusions if we are deprived of sensory inputs altogether (Vosburg et al., 1960).

There are other examples of illusions in the absence of sensory stimuli, from less controlled and more complex (e.g. phantom pain (Blakeslee & Ramachandran, 1998), or illusory percepts in a scotoma) to fully controlled (e.g. magnetic pulse-induced ‘phosphenes’; illusory visual experiences induced without visual stimulation (de Graaf, Koivisto, Jacobs, & Sack, 2014)). Goebel et al. (1998) provided a compelling demonstration of how to use illusions to study conscious perception. They used static visual stimuli to induce illusory contours that appeared to move (the illusory motion quartet), and mapped correlating brain activity with fMRI. By separating the features of the visual inputs (static) from the features of the illusory percept (motion), the activity observed in the human motion areas could only be attributed to the endogenous construction of conscious motion perception.

*Multistable paradigms* notably include the well-researched paradigms of binocular rivalry (Blake, 2001; Fox, 1991), and ambiguous figures, such as the famous Necker cube or Rubin’s vase/faces (see Figure 1). In the *binocular rivalry*

paradigm, two different images are presented, each to one eye, at corresponding retinal locations. They need to be sufficiently different from each other, so that binocular fusion is impossible. As a result, the conscious percept of the observer keeps changing, even though stimulation never changes. Similarly, an observer will always experience only one conscious percept at a time when presented with a constant *ambiguous figure*, such as Rubin's vase/faces (Figure 1B), where the observer either experiences the vase, or the face, but never both simultaneously. In binocular rivalry, and here, comparing brain activity during both possible percepts can be very useful to find NCC's, because there is a change in consciousness unaccompanied by a change in external inputs. Any change in brain activity, occurring together with the change in consciousness, can be interpreted as underlying conscious processing of whichever percept is now reported. These correlates of conscious percepts are then not confounded by several unconscious perceptual processes that normally result from changes in inputs.

However, in those multistable paradigms, a condition is defined by the participant's report of their conscious percept. Participants mainly signal their experience by button presses. Practically, this creates problems in neuroimaging, since brain activity correlated to such percept switches (Lumer, Friston, & Rees, 1998; Tong & Engel, 2001) is contaminated with task performance (Knapen, Brascamp, Pearson, van Ee, & Blake, 2011). With M/EEG, the variability in response times creates additional difficulty (Strüber, Basar-Eroglu, Hoff, & Stadler, 2000; Strüber & Herrmann, 2002), so it is promising that new and temporally accurate measures of percept switch timing are being explored (e.g. ocular reflexes; Frässle, Sommer, Jansen, Naber, & Einhäuser, 2014).



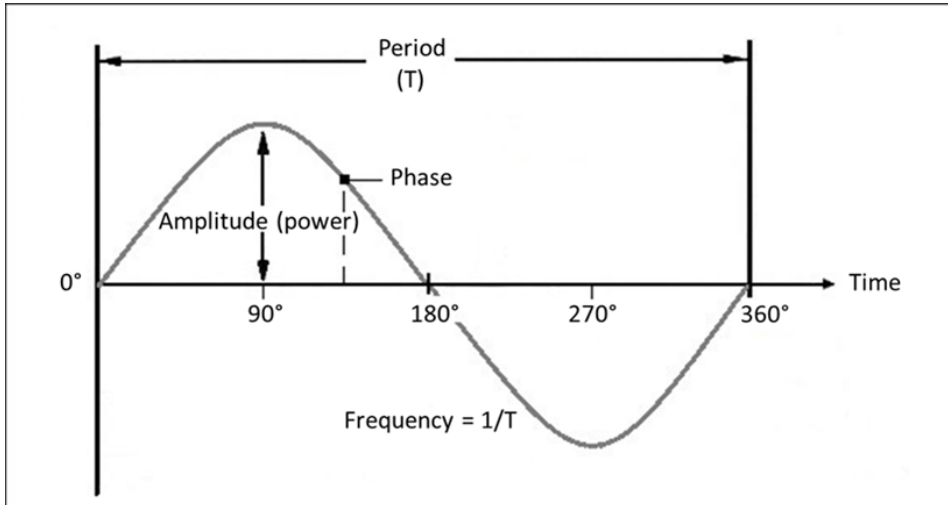
**Figure 1:** Experimental paradigms. Three different examples of consciousness paradigms: a) *Illusions*. The Kanizsa triangle consists of three spherical figures, each of which misses a triangular portion (pac-men). When placed in a proper configuration the figures induce an illusory percept of triangle-contours (Kanizsa, 1976). b) *Multistable paradigms*. The vase/faces figure provides a well-known demonstration of bistable perception: the same visual stimulus can alternately induce the perception of either a vase or two faces (Rubin, 1915). c) *ON-OFF paradigms*. The visual masking paradigm, for example, uses two stimuli presented in spatiotemporal proximity. Depending on the time between them (stimulus onset asynchrony, SOA) the participant is conscious (ON) or not conscious (OFF) of the vertical grating.

The high temporal resolution of M/EEG makes these techniques particularly well-suited for a third class of consciousness paradigms: *ON-OFF paradigms*. ON-OFF tasks have two conscious states: ‘stimulus perceived’ (ON) and ‘stimulus not perceived’ (OFF), i.e. conscious vision present vs not present. The implementations of this basic principle come in many forms, such as visual masking (Breitmeyer & Ogmen, 2006) or transcranial magnetic stimulation (TMS) (Taylor, Walsh, & Eimer, 2010). Generally, brain activity is simply contrasted between the ON and the OFF condition. Hemodynamic imaging allows us to study consciousness using ‘weak ON-OFF tasks’ in which *small stimulus parameter adjustments* cause stimuli to be always perceived or never perceived – enabling the implementation of experimental blocks of ON and OFF trials (e.g. word masking in Dehaene et al., 2001). But M/EEG can employ ‘strong ON-OFF tasks’ in which the *exact same stimuli* are used in all trials. In this case, brain activity highlighted by contrastive analysis is strictly related to endogenous processes differentiating stimulus perceived (ON) from not perceived (OFF) conditions, since the input does not change at all. With strong ON-OFF tasks we can therefore isolate and compare even more precisely the activity related to the two conditions. As per our earlier example; the simplest form of this is visual stimuli presented at perception threshold, causing detection (ON) on half of all trials, and failure to detect (OFF) on the other half of trials.

Thus, illusions, multistable, and ON-OFF paradigms, are all suitable for brain imaging experiments employing contrastive analysis. Yet they also share a conceptual difficulty which should be noted. In the example of a stimulus detection task, ON trials can engage a neural mechanism ‘N’, which is not activated in OFF trials. ‘N’ is therefore an empirical correlate of consciousness. But which level of processing is ‘N’ involved in? A conscious percept finally arises from a cascade of processing, much of which is unconscious and which can likely be segmented into many steps and stages depending on context and framework. Thus, the exact *role* of ‘N’ can usually not be determined from a single experiment. We return to this issue in section “functional roles of oscillatory NCCs”.

### 2.2.2 Oscillations

To continue with the example of a detection task, once ON and OFF trials have been post-hoc labeled based on participant responses, oscillatory activity can be contrasted between both conditions. Though we will discuss primarily oscillatory activity as measured with non-invasive neuroimaging methods such as M/EEG, much will apply to oscillatory signals measured more invasively in humans (e.g. electrocorticography; ECoG) or oscillatory signals from smaller populations (e.g. local field potentials). So what is ‘oscillatory activity’? A single oscillating signal can be characterized by three parameters: frequency, amplitude, and phase.



**Figure 2:** Oscillation parameters. *Frequency*: Number of cycles per unit of time (s). *Amplitude*: Strength of the signal (size of deflections from the mean). *Phase*: Momentary position on the cycle at a certain point in time. *Period*: Time duration of one cycle.

The rhythmic fluctuations in M/EEG signals primarily reflect rhythmic synchronous firing of populations of pyramidal neurons (i.e. excitatory and inhibitory postsynaptic action potentials (Creutzfeldt, Watanabe, & Lux, 1966; Proudfoot, Woolrich, Nobre, & Turner, 2014)). The strength of the signal, which translates to the *amplitude* (directly related to ‘power’) of an oscillation, depends on the absolute number of firing pyramidal cells, how often they fire, and to what extent they fire synchronously. This synchronization is mainly guided by interneurons which, discharging together, generate perisomatic inhibitory postsynaptic potentials (Bartos, Vida, & Jonas, 2007). The rhythmic nature of individual neuronal firing bursts results in population-level activity that follows a sinusoidal pattern, with alternating high and low levels of activity. At any point in time, where (or rather when) the signal finds itself on this repeating sinusoidal activity cycle is defined as its *phase*. How often the activity cycle goes up and down in a certain unit of time (generally seconds) is defined as the signal’s *frequency*, see Figure 2 for a visualization.

When looking at an oscillating signal across repeated trials, one could analyze how similar the phase is across trials with reference to a particular time-locked event; called *phase-locking* (Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). When looking at brain systems, one could also evaluate phase-locking between two nodes of a brain network, evaluating how consistent the phase relationship is between two oscillating signals when a particular event occurs. Or, more generally, and independently of certain time-locking occurrences, how consistent the phase relationship is between two ongoing signals from two brain regions, in which case one is quantifying *phase coherence* (Srinivasan, Russell, Edelman, & Tononi, 1999). Such measures likely reflect functional connectivity between regions, and while there is a whole range of more advanced analyses one might consider in such contexts, for instance to evaluate directed connectivity (which region drives activity in the other?), these are beyond the scope of this review (see Bastos & Schoffelen, 2015 for a recent review of advanced analyses).

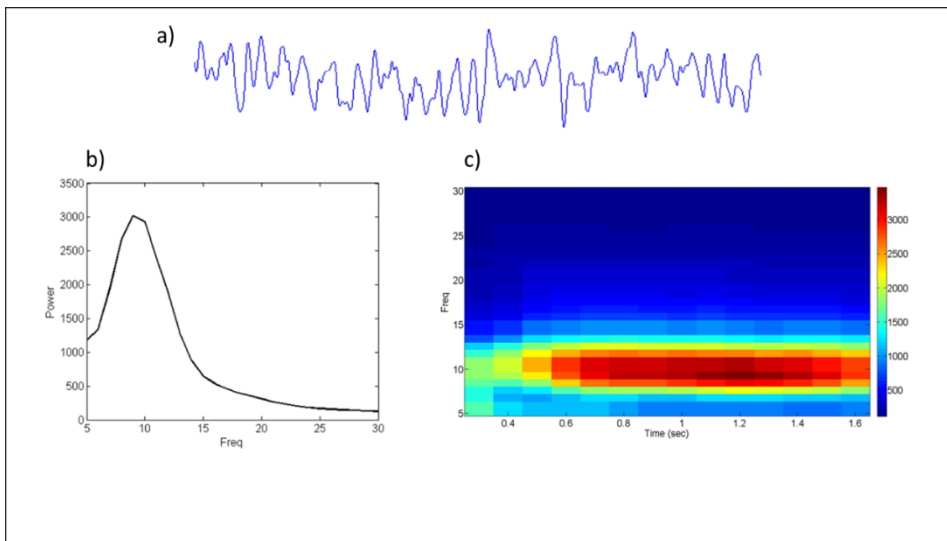
Data obtained with M/EEG measurements reflect a combination of noise and signals, which can be analyzed in different ways. As shown in Figure 3, one can extract the contribution of oscillatory signals in different frequencies (Figure 3B) to the original (preprocessed) data (Figure 3A), or visualize how these contributions change over time (Figure 3C). Oscillatory brain activity itself can fluctuate over time, and different networks in the brain are characterized by different frequencies (Keitel & Gross, 2016). For instance, occipital and parietal brain areas are mostly characterized by alpha activity, and sensory areas by alpha as well as beta activities (Hari & Salmelin, 1997; Hillebrand, Barnes, Bosboom, Berendse, & Stam, 2012; Pfurtscheller, Stancák, & Neuper, 1996). Furthermore, it has been suggested that activity within a given brain network may reflect a unitary sampling rhythm that is different between distinct networks (Canolty &



Knight, 2010). For example, while small local networks usually operate in higher frequencies, larger distributed networks may employ slower fluctuations (Draguhn & Buzsaki, 2004). In line with this idea, theta/alpha-band oscillations (4-13 Hz) have been related to long-range communication, but beta/gamma-band oscillations (20-100 Hz) to short-range signaling (von Stein, Chiang, & König, 2000).

Moreover, certain brain systems may inherently prefer different frequency-bands, referred to as their ‘normal frequencies’ (Niedermeyer, 1999). In fact, different brain systems show particularly strong responses in different frequency-bands, measured with EEG, in response to single magnetic pulses (TMS), with occipital cortex presenting a stronger response to alpha-band oscillations, parietal cortex to beta-band oscillations and frontal regions to fast beta and gamma oscillations (Rosanova et al., 2009). But it has also been suggested that brain networks might be flexible enough to employ different frequencies depending on sensory modality, task demands or parameters (VanRullen, 2016). In sum, the engagement of oscillatory mechanisms in distinct frequency bands across regions, tasks, and brain states, remains a topic of intense investigation.

This completes our introductions into consciousness paradigms, oscillation signals, and (analysis of) oscillatory brain mechanisms. In what follows, we review current evidence for oscillatory mechanisms that correlate with conscious (visual) perception.



**Figure 3:** From EEG time-signal (a) to a frequency (b) or even time-frequency (c) representation. A. the time signal reflects how much signal (voltage) is picked up at an electrode/sensor at subsequent sample points. B. a Fourier analysis can reveal to what extent (power; vertical axis) sinusoids in different frequencies (horizontal axis) contribute to it. C. similar analysis can reveal the development (time; horizontal axis) of such frequency (vertical axis) contributions (color-coding).

## 2.3 OSCILLATORY CORRELATES OF CONSCIOUSNESS

We have seen that there is a range of paradigms to study oscillatory NCCs, and a range of oscillatory parameters to evaluate. In this section we will review key findings on oscillatory correlates of consciousness, grouped by frequency-band. Lower frequencies (delta, theta) do not have a dedicated section because we are not aware of much evidence supporting their role in conscious vision per se.

### 2.3.1 Gamma frequency

Experimental evidence for a relationship between gamma-band (high-frequency: ~30-100 Hz) activity and conscious perception was highly influential, helping to reinvigorate the scientific study of consciousness when Crick and Koch (1990a) summarized it in the '40 Hz hypothesis'. This hypothesis proposed that distributed neuronal activity is 'bound' through synchronization of oscillations, and that such synchronized activity specifically in the gamma-band is a neural correlate of conscious perception. Engel and Singer (2001) noted that binding by synchrony is implicated in several major processes related to conscious perception; arousal (Munk, Roelfsema, König, Engel, & Singer, 1996), segmentation (Engel, König, & Singer, 1991), selection (Fries, Roelfsema, Engel, König, & Singer, 1997), and working memory (Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). In cats, global features of visual stimuli (i.e. coherency of motion) produced gamma synchronization in the visual cortex (40-60 Hz) (Gray, König, Engel, & Singer, 1989). Moreover, gamma-band synchrony directly indexed which of two incompatible images was perceived by a cat in a binocular rivalry implementation (Fries et al., 1997). In macaques, local field potential (LFP) fluctuations in the gamma range were recently correlated to phenomenal perception, higher up in the visual hierarchy in lateral prefrontal cortex (Panagiotaropoulos, Deco, Kapoor, & Logothetis, 2012).

In humans, M/EEG studies showed that synchronization between large populations of neurons in anterior and posterior brain areas correlates to conscious vision (Srinivasan et al., 1999), occurring at global rather than local level as, for instance, it happens during the encoding of an external stimulus from a sensory area (Ward, 2003). Words that are consciously perceived, as compared to words not perceived, lead to a transient distributed gamma synchronization response, phase-locked both across and within hemispheres (Melloni, Molina, Pena, Torres, Singer, & Rodriguez, 2007). Furthermore, long-distance gamma synchronization appears only when perceptual objects are perceived as coherent conscious percepts (i.e. faces) as opposed to meaningless shapes (Doesburg, Kitajo, & Ward, 2005; Rodriguez & George, 1999).

Gamma-band activity and consciousness have been investigated extensively, but not exclusively, in the visual domain. Gamma synchronization also correlates with conscious perception of non-visual stimuli. For example in the auditory system oscillatory activity near 40 Hz is not only related to the sensory but also to the cognitive processing of auditory clicks stimuli (Joliot, Ribary, & Llinás, 1994). Furthermore, it has been related also to multimodal perception (Senkowski, Schneider, Foxe, & Engel, 2008). For example, a recent study used a paradigm consisting of visual and auditory stimuli and showed that gamma power correlates with audiovisual perception (Balz et al., 2016). It can also have a functional role in the binding of distributed neural activities in olfactory consciousness (Mori, Manabe, Narikiyo, & Onisawa, 2013). Lastly, tactile stimulation of one hand increases gamma-band coherence in the contralateral primary somatosensory cortex only when the stimulus is consciously perceived (Meador, Ray, Echauz, Loring, & Vachtsevanos, 2002) as well as when tactile stimuli are associated to visual stimuli, showing contralateral enhancement of gamma-band activity in occipital cortex (Lange, Oostenveld, & Fries, 2011).

In spite of these examples, gamma oscillatory activity as a ‘signature’ of consciousness continues to be debated. Gamma synchronization may also be induced by processes such as attention (Fries, Roelfsema, Engel, König, & Singer, 1997), which should be separated from conscious perception whenever possible (Koch & Tsuchiya, 2007). In this context, Wyart and Tallon-Baudry (2008) have suggested that attention is more associated with high gamma frequency, whereas conscious perception is more associated with mid-range gamma synchronization. Yet, there is also evidence that gamma-band activity does not solely appear when consciousness is present but can also persist or even increase during anesthesia (Imas, Ropella, Ward, Wood, & Hudetz, 2005; Murphy, Bruno, Riedner, Boveroux, Noirhomme, & Landsness, 2011; Vanderwolf, 2000) or seizures (Pockett & Holmes, 2009), brain states that are clearly not characterized by consciousness. It may therefore be that although gamma-band activity is present in many different conscious states, it is not exclusive to them (Hermes, Miller, Wandell, & Winawer, 2015) and not sufficient to allow consciousness (Luo et al., 2009). Of course different measures of gamma-band activity have been considered in the past, from local gamma power to distributed gamma coherence, and moreover in and across different brain systems, so the picture remains incomplete.

### 2.3.2 Beta frequency

One example of an ON-OFF paradigm is the ‘attentional blink’ paradigm, in which a rapid stream of visual stimuli is presented at fixation (rapid serial visual presentation, RSVP, task). Participants are given two targets (i.e. specific

letters) to watch out for, and press a button whenever they see either one of them. The attentional blink phenomenon is the observation that participants are more likely to miss a target, if it follows a preceding target in a particular temporal window (target 1 to target 2 onset asynchrony (stimulus onset asynchrony, SOA) of around 200-500 ms; Shapiro, Raymond, & Arnell, 1997). The ‘weak’ version of this paradigm uses two different SOAs, one leads to stimulus perception (ON) and one does not (OFF). When only one SOA is used, for which target 2 is sometimes detected and other times not, this paradigm becomes a ‘strong’ ON-OFF paradigm. Gross et al. (2004) measured MEG during such an implementation. They found increased power in the low beta-band during the entire stream of stimuli when targets were detected (ON) compared to when they were not (OFF). Furthermore, they found stronger beta synchronization in a network dominated by right inferior parietal and left prefrontal regions, in ON trials.

The enhancement of beta synchronization might reflect a general state of increased sensitivity to behaviorally relevant stimuli, which could explain better target detection performance. Gaillard et al. (2009) presented masked words at threshold contrast, in an intracranial EEG study. In detected versus non-detected trials, there was stronger beta synchronization between long-distance regions, especially during the late phase of the conscious access, whereas this coherence was suppressed when the same stimulus does not become conscious. Interestingly, in both studies the synchronized activity appears not only in posterior regions, but spreads in a broader network that involves also frontal areas.

The relationship between beta oscillations and visual consciousness is not yet fully clear. For instance, one recent study with invasive recordings in the macaque, showed that the power of beta oscillations in lateral prefrontal cortex is not modulated by conscious versus unconscious stimulus processing (Panagiotaropoulos, Kapoor, & Logothetis, 2013). But here again, we should keep in mind that local oscillatory synchronization, i.e. local oscillatory power, may reflect at least partially non-overlapping brain processes as compared to measures of phase coherence. Synchronization across brain regions is not the same as synchronization within brain regions.

## 2.4 ALPHA-BAND ACTIVITY

Alpha oscillations have been extensively researched in relation to conscious (visual) perception. The alpha rhythm (7-13 Hz) is strongly linked to posterior areas of the brain, and has been associated to input regulation (Lorincz, Kékesi, Juhász, Crunelli, & Hughes, 2009) as well as attention (Kelly, Lalor, Reilly, & Foxe, 2006; Marshall, O’Shea, Jensen, & Bergmann, 2015; Sauseng et al., 2005;

Thut, 2006; Worden, Foxe, Wang, & Simpson, 2000). When our brain is not engaged in a particular task, oscillations with alpha rhythm are more prominent and easy to detect, leading to the notion that alpha is an ‘idling’ rhythm, the activity of the brain at rest (Pfurtscheller et al., 1996). For instance, simply closing the eyes strongly enhances alpha power (Berger, 1929). At the same time, a large body of research has led to several sophisticated theories on exactly which role alpha activity plays in attention, perception, and awareness. Below, we discuss in turn several parameters of alpha activity and how they have been studied using versions of consciousness paradigms.

### 2.4.1 Alpha power

Since ongoing alpha power does not stay at a constant level but fluctuates over time (Lopes da Silva, 1991), alpha power fluctuations have been studied in relation to fluctuations in visual target detection. For instance, across participants, Hanslmayr et al. (2005) showed that lower performance in a visual perception task, in which participants discriminated different letters, correlated to higher parieto-occipital alpha amplitudes. Also within participants, the higher pre-stimulus alpha power activity, the less likely it is that a stimulus is detected. This probability of detection can be predicted by the amount of pre-stimulus alpha power trial-by trial (Ergenoglu et al., 2004), particularly from alpha signals originating in the parieto-occipital sulcus (van Dijk, Schoffelen, Oostenveld, & Jensen, 2008). One interpretation of these results suggests that alpha power indexes a state of excitability (Klimesch, Sauseng, Hanslmayr, 2007). Indeed, Lange, Oostenveld & Fries (2013) cleverly used so-called ‘double flash illusion’ and ‘fusion effect’ paradigms to distinguish whether reduced alpha power increases the accuracy of visual processing (correctly reporting the occurrence of either one or two stimuli) or rather increases visual excitability (reporting two stimuli irrespectively of the correct answer). Their findings supported the latter hypothesis.

It has been suggested that a more direct measure of visual cortex excitability can be derived from phosphene perception. Phosphenes are fleeting conscious visual experiences, elicited experimentally through direct stimulation of visual cortex (Marg & Rudiak, 1994). For instance, TMS can be used to non-invasively excite neurons in occipital cortex, which in many participants results in phosphene perception if the stimulation intensity is sufficient. Different levels of excitability can be assessed directly by evaluating the stimulation intensity required to elicit phosphenes (phosphene threshold), or the proportion of trials that results in phosphene perception at some fixed level of stimulation intensity. A lower phosphene threshold, or higher proportion of phosphene perception at fixed TMS intensity, indicates higher visual excitability. Measuring alpha power with EEG, and visual excitability with TMS, alpha power has been related to

excitability (with higher alpha power indicating lower excitability) across (Romei, Rihs, Brodbeck, & Thut, 2008b) and within (at trial-by-trial level) participants (Romei, Brodbeck, Michel, Amedi, Pascual-Leone, & Thut, 2008a).

In sum, converging evidence suggests that the power of alpha oscillations around stimulus (or TMS pulse) onset co-determines whether that stimulus reaches conscious perception.

#### 2.4.2 Alpha phase

Inherently, oscillatory phase fluctuates more quickly than power. In the case of alpha-band oscillations, several studies have correlated visual detection performance to the phase of naturally occurring alpha oscillations at the moment of target presentation. Busch et al. (2009) showed that the threshold to detect light flashes covaries over time with alpha phase, suggesting that alpha phase might shape our perception by determining whether or not a visual stimulus is selected for awareness. Similarly, Mathewson et al. (2009) revealed that metacontrast-masked visual targets are more likely to be detected if targets are presented at the peak, as opposed to the trough, of ongoing alpha oscillations measured with EEG. Interestingly, they found that alpha phase predicted detection performance only when alpha amplitude was high. Thus, oscillatory phase and amplitude, though different measures, may be challenging to evaluate separately.

It is possible that, as we saw above for alpha power, also alpha phase directly reflects visual excitability. Once again, TMS-elicited phosphene perception has been used as a probe for occipital excitability. And indeed, phosphene perception, and thus visual excitability, depend on the phase of ongoing alpha oscillations (Dugué, Marque, & VanRullen, 2011). At the same time, it has been suggested that alpha oscillations represent the time frames of perception (VanRullen, 2016): short visual ‘snapshots’ of the world are represented by single cycles of the alpha oscillation. This hypothesis has been supported by studies showing that two visual stimuli presented in a short period can be detected as one, or two, depending on the precise frequency of alpha oscillations in individual observers. The shorter the cycle is (higher individual alpha frequency (IAF)), the higher the temporal resolution of perception will be, and thus the more likely it will be that an observer can correctly detect the presentation of two separate stimuli over time (Samaha & Postle, 2015), independently of the amplitude of alpha-band activity (Milton & Pleydell-Pearce, 2016).

There is further evidence for a functional role of alpha phase in the context of conscious vision, stemming from a different category of studies to which we now turn.

## 2.5 IS OSCILLATORY ACTIVITY CAUSALLY INVOLVED IN VISUAL CONSCIOUSNESS? ENTRAINMENT APPROACHES

The studies discussed so far have utilized a correlational approach, generally contrasting passively measured brain activity in trials in which a stimulus was perceived with trials in which a stimulus was not perceived. Such studies have clearly shown that oscillatory activity, namely power, phase, and coherence in distinct frequency bands, can be related to conscious vision. They do not clarify, however, whether such electrophysiological processes play a causal role in perception and awareness, or are epiphenomenal consequences of other brain mechanisms that underlie conscious perception. To evaluate the causal role of oscillations, one should find a way to manipulate oscillatory parameters externally, bringing neuronal oscillations under experimental control. This general approach is called ‘*entrainment*’ (Herrmann, Strüber, Helfrich, & Engel, 2016; Thut, Schyns, & Gross, 2011a), and can be achieved in different ways. These include rhythmic sensory stimulation and brain stimulation. Here we briefly review evidence that these approaches can indeed affect behavioral performance and neuronal oscillations, followed by an overview of which oscillations appear to be causally relevant for conscious vision.

### 2.5.1 Entraining behavior

A participant presented with a stream of auditory stimuli, in a constant rhythm, can predict when an upcoming stimulus will appear. This phenomenon may be related to ‘*sensory entrainment*’; the alignment of a sensory system to the rhythm of sensory stimulation (Sameiro-Barbosa & Geiser, 2016). To test whether the sensory system of the participant is aligned with an external stimulation, researchers measure task performances as, for example, reaction time or detection accuracy. When the synchronization to the rhythm of presentation occurs, the response to an upcoming external stimulus is typically faster (i.e. lower reaction time), compared to when the entrainment is not present.

Rimmele, Jolsvai & Sussman (2011) used auditory stimuli in order to test whether spatial and temporal expectations may change task performance. They used four different conditions (temporal expectation, spatial expectation, temporal and spatial expectation, no expectation) and showed enhanced target detection and faster reaction time only in the condition of stimuli presented with temporal regularity. Furthermore, entrainment may lead to a more accurate performance. Facilitated performance has been shown in discriminating the intensity of a tone (Jones, Moynihan, MacKenzie, & Puente, 2002), as well as its duration (McAuley & Jones, 2003). In the visual domain, when gabor patches

were presented within a stream of stimuli with fixed SOA, they were discriminated better compared to when SOAs in the stream were jittered (Rohenkohl, Cravo, Wyart, & Nobre, 2012). The same results have been shown by Marchant & Driver (2013) who, using auditory (tones) and visual (red annuli) stimuli, showed faster reaction times and improved visual sensitivity when they were presented in an isochronous (with temporal regularity) condition compared to when they were presented randomly.

### 2.5.2 Entraining oscillations

An important question is whether this temporal alignment (i.e. synchronization) occurs not only at behavioral level, but also between intrinsic neural activity and the rhythm of the external stimulation. Oscillatory brain activity can be entrained by stimuli of different nature (e.g. visual, auditory, tactile) which may lead to synchronization of neural activity in visual (de Graaf et al., 2013; Mathewson et al., 2012), auditory (Besle et al., 2011; Luo & Poeppel, 2007; Nozaradan, Peretz, & Keller, 2016) or somatosensory (Langdon, Boonstra, & Breakspear, 2011; Ross, Jamali, Miyazaki, & Fujioka, 2013; Ruzzoli & Soto-Faraco, 2014) brain areas. Oscillations in different frequency bands can be synchronized to external stimuli depending on the rhythm of stimulation (Lakatos, Musacchia, O'Connell, Falchier, Javitt, & Schroeder, 2013; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008). Rhythmic auditory stimulation, for example, can modulate neural activity in high frequency bands as beta and gamma (Fujioka, Trainor, Large, & Ross, 2012; Snyder & Large, 2005) and even more robustly in low frequencies as delta and theta (Ding, Chatterjee, & Simon, 2014; Howard & Poeppel, 2012; Kayser, Montemurro, Logothetis, & Panzeri, 2009).

One shortcoming of sensory entrainment is that it can be difficult to localize the brain mechanisms underlying its effects. After all, the rhythmic sensory stimuli are processed throughout a sensory system, making it difficult to evaluate the causal role of oscillations in a specific brain area of interest. Fortunately, it is also possible to entrain neuronal oscillations locally, by *directly* stimulating a brain region with a particular frequency. *Non-invasive brain stimulation* (NIBS) has been applied to study the causal contribution of brain areas to a wide variety of processes (including conscious vision, see for review: de Graaf & Sack, 2014), and recently also brain oscillations.

TMS and transcranial alternating current stimulation (tACS) are NIBS techniques used to entrain neuronal oscillations (Antal et al., 2008; Thut et al., 2011). Single TMS pulses have been shown to affect oscillatory mechanisms in distinct frequency bands depending on the site of stimulation (Rosanova et al., 2009). When multiple TMS pulses are applied in a certain frequency (e.g. 10 Hz), this likely causes a resetting of the phase of oscillatory neural activity followed



by amplification of local oscillatory power in that same frequency range (Thut et al., 2011).

TACS uses a low-intensity alternating current (i.e. it changes direction periodically) which can affect the membrane potential. Thereby it can interact with cortical excitability, allowing the modulation of spontaneous brain activity in specific frequencies (Antal, Boros, Poreisz, Chaieb, Terney, & Paulus, 2008; Chaieb, Antal, & Paulus, 2011; Wach et al., 2013). Zaehle, Rach and Herrmann (2010) showed that when tACS is applied at IAF, its effects last beyond the stimulation, resulting in enhanced alpha power as measured by EEG after versus before tACS. Neuling et al. (2013) suggest that the after-effect can last up to 30 minutes, but emerges only when tACS amplitude is greater than the endogenous IAF power. Also using an online paradigm (i.e. the stimulation is applied while EEG records neural activity), Helfrich et al. (2014) could show that oscillatory entrainment at 10 Hz in parieto-occipital areas increases alpha power. However, it appears relevant that tACS is continuous. Strüber et al. (2015) used a short intermittent protocol composed of 1.5 seconds of resting EEG and 1 second of tACS stimulation, showing that such short stimulation bursts did not cause entrainment.

Despite the substantial number of studies reporting entrainment, the mechanisms underlying the effect of tACS is still not completely clear. For example, the effects may depend on brain state during stimulation, such as having eyes open or closed (Ruhnau, Neuling, Fuscá, Herrmann, Demarchi, & Weisz, 2016). Furthermore, Vossen, Gross and Thut (2015) replicated with EEG that alpha frequency tACS increased power in the alpha band (for repeated 8 second but not 3 second bursts of tACS). However, these after-effects of tACS were observed independently of whether sequential bursts of tACS were in phase or not. Also, EEG alpha oscillations immediately following tACS bursts did not phase-align with the preceding tACS burst. Lastly, the peak frequency in the alpha band after tACS did not correspond well with the exact tACS frequency, rather reflecting individual alpha frequency. These results led the authors to propose a different hypothesis regarding the after-effects of tACS stimulation; reflecting synaptic plasticity rather than entrainment.

### 2.5.3 Causal role of oscillations for conscious vision

In sum, both behavior (i.e. task performance) and neuronal oscillations can be affected by rhythmic sensory stimulation or rhythmic brain stimulation. Have these techniques been applied to oscillatory correlates of consciousness? If human brain oscillations can be controlled through entrainment approaches, oscillatory power and phase in specific frequencies become independent variables, allowing us to probe their causal role in conscious vision.

Using visual stimuli, Mathewson et al. (2010) found that detection

performance depends on the latency of target presentation relative to a preceding rhythmic visual cue train. In fact, visual perception performance can oscillate across multiple alpha cycles following an alpha cue train (de Graaf et al., 2013; Mathewson et al., 2012). It seems likely that phase-reset/-locked neuronal alpha oscillations underlie such patterns of visual performance, as even a single sound can induce visual excitability fluctuations with alpha frequency (Romei, Gross, & Thut, 2012).

In a pioneering study, Romei et al. (2010) showed that a burst of TMS pulses applied at 10 Hz directly affected whether or not a subsequent visual target was perceived. TMS pulses applied at different frequencies (5 or 20 Hz) had no such effect. Presenting visual targets at different latencies from a rhythmic alpha TMS burst also modulated target perception, suggesting that not only alpha power, but also alpha phase is causally relevant (Jaegle & Ro, 2014). Chanes et al. (2013) used TMS to entrain high-beta (30 Hz) or gamma (50 Hz) frequencies. They showed that neural activity was entrained only when these two specific frequencies were used, but not when the stimulation did not have a specific rhythm (used as control conditions). Depending on the frequency of stimulation, specific behavioral aspects of task performance were altered, such as perceptual sensitivity and response criterion.

The causal role of oscillatory activity in conscious vision has also been studied with tACS. Helfrich et al. (2014) suggest that tACS-entrained alpha phase is relevant for visual perception. Kanai et al. (2008) reported that with ambient light, it is possible to induce phosphenes with occipital tACS at beta frequency. In contrast, in darkness, phosphenes were more likely perceived with tACS at alpha frequency. In a recent study, a ‘square’ of two sets of diagonal light stimuli were presented in alternation (a ‘motion quartet’). In this bistable apparent motion stimulus, two lights could be perceived as moving back and forth horizontally, or vertically. TACS was applied at 40 Hz over both occipital cortices. The stimulation led to a relative decrease in horizontal motion perception, but only if the two hemispheres were stimulated with a 180 degree phase difference (i.e. anti-phase) and not with 0 degree phase difference (in-phase) (Strüber, Rach, Trautmann-Lengsfeld, Engel, & Herrmann, 2014).

In sum, entrainment approaches allowing researchers to control the power or phase of oscillations at a particular frequency have indeed been applied to conscious vision paradigms. But at the same time, comparing these studies with the overview of oscillatory correlates makes clear that 1) many oscillatory correlates of consciousness remain to be tested causally using entrainment techniques, and 2) the reviewed entrainment studies have focused predominantly on local power and phase, while conscious perception might depend (also) on more complicated oscillatory mechanisms, such as widespread coherence. Therefore, it seems useful to quickly review some of the exciting recent developments in entrainment methodology, which may open up causal studies of

oscillatory mechanisms of consciousness even further.

### 2.5.4 Advanced entrainment approaches

Polania et al. (2012) successfully manipulated oscillatory *coherence* between frontal and parietal cortex in a memory task, using tACS. Experimentally synchronizing oscillations in the theta (6 Hz) band (applying tACS over both regions with 0 degree phase difference) improved working memory performance, while experimentally desynchronizing oscillations (tACS over both regions with 180 degree phase difference) impaired performance. In another application, Alekseichuk et al. (2016) recently modulated *cross-frequency coupling*, showing that gamma bursts coinciding with theta-peaks improved working memory performance, while this effect was absent if gamma bursts coincided with theta-troughs. This experimental manipulation was achieved with tACS stimulation, with short bursts of gamma-signals superimposed on an ongoing theta-signal.

In principle, such sophisticated tACS entrainment approaches require only an appropriate electrode montage, and equipment that allows external control of electrical stimulators. A complex electrical waveform such as required for cross-frequency coupling modulation can ‘simply’ be programmed and fed into the stimulation devices. Also the presentation of stimuli in single or multiple modalities can be time-locked to one or multiple tACS waveforms, to for example consistently present certain inputs at certain phases. We recently discussed hardware and freely available software solutions to enable such experiments (ten Oever et al., 2016). While the examples discussed directly above did not relate to conscious vision, most of the oscillatory correlates of consciousness reviewed here could be causally studied with entrainment, using such available tools.

## 2.6 FUNCTIONAL ROLES OF OSCILLATORY NCCS

Oscillatory mechanisms that covary with conscious experience are, by definition, NCC. Such empirical findings can be called ‘empirical NCCs’ (de Graaf & Sack, 2015). But it has been repeatedly noted that finding empirical NCCs is not the end goal. An empirical NCC can still fulfil different functional roles, which should be understood in order to move forward to understanding how the brain actually establishes conscious experiences (Aru, Bachmann, Singer, & Melloni, 2012b; Bachmann, 2009; Hohwy, 2009; Kanai & Tsuchiya, 2012; Melloni & Singer, 2010; Miller, 2001; 2007; Noë & Thompson, 2004; Sergent & Naccache, 2012). In the context of oscillatory correlates of consciousness, this is exactly

why entrainment approaches are so valuable; they allow us to go beyond correlation.

### 2.6.1 Prerequisites, substrates, consequences

Several authors proposed different frameworks with possible roles that neural correlates, including oscillatory correlates, may play. What they appear to have in common, at least on a conceptual level, is that among the wealth of empirical neural correlates, only some reflect conscious experience itself.

Sergent & Naccache (2012) discuss the Global Workspace model (see also (Baars, 1989; Dehaene & Naccache, 2001; Dehaene, Changeux, Naccache, Sackur, & Sergent, 2006), postulating that many brain networks are continuously active, processing incoming information unconsciously. When top-down attention comes into play and leads to non-transient coherent activity throughout the brain, information can become conscious. In a first step, at low-level areas in the visual hierarchy (e.g. primary visual cortex) for about 200 ms after presentation of the stimulus, visual information is not yet conscious ('upstream processing'). As the information spreads to higher-order areas (i.e. frontal lobes), in a second step we can reach 'ignition' of the global workspace. Ignition means that we will have conscious experience on the one hand, and several 'downstream' processes that result from conscious experience and its underlying neural signature on the other hand. These can be hard to distinguish.

In another framework, Ruhnau, Hauswald & Weisz (2014) suggest that the parameters of power and phase are useful to describe local excitability and consequent stimulus detection, but not sufficient to thoroughly explain conscious experience. In fact, they propose that other networks in the brain (connected to high-order areas, i.e. parietal and prefrontal) need to be pre-activated to open a so-called "window to consciousness" (*Win2Con*) and allow conscious perception. Local cortical excitability seems to be a "prerequisite" for conscious perception but does not reflect its neural process. General brain connectivity (from local to global level) seems to be required for visual consciousness, leading to conscious experience only when integration of relevant areas is achieved.

We and others (Aru, Bachmann, Singer, & Melloni, 2012a; de Graaf et al., 2012; de Graaf & Sack, 2014) suggest that to define (and refine) correlates of consciousness it is useful to distinguish three core roles of an empirical NCC: neural *substrates*, neural *prerequisites*, and neural *consequences* of a conscious experience. 'Substrates' are the 'actual' NCC of interest, in the sense that the neural substrates of experience are directly causing, or are identical with, the phenomenal conscious experience. 'Prerequisites' are the neural events and mechanisms that are needed for neural substrates (and thus for a conscious experience) to arise. Consequences are in a sense less interesting, because they merely occur as a side-product of the neural prerequisites/substrates, however

meaningful in a cognitive/behavioral sense they may be. All the same, only a correct understanding, or even allocation, of empirical NCCs in light of these three different ‘roles’ can lead to a complete model of brain-experience relationships. Looking at the other examples of theoretical frameworks, it is easy to draw parallels. So we will continue to use our own terminology to refer to, for instance, ‘prerequisites’ rather than ‘upstream processes’, even if similar conclusions could arise.

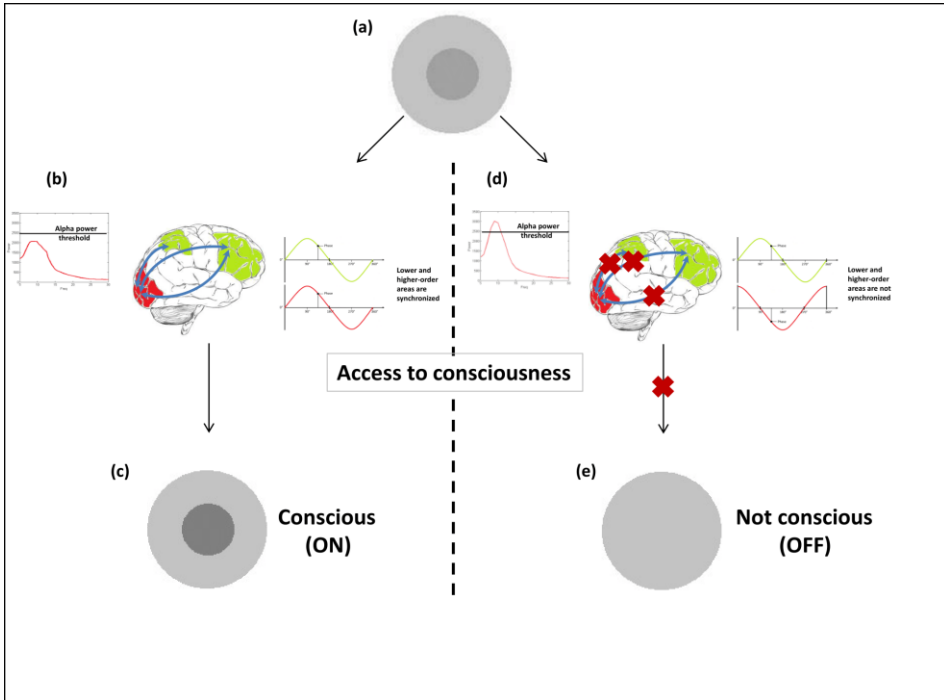
### 2.6.2 Oscillatory prerequisites, substrates, and consequences?

It might be useful to evaluate how this taxonomy maps onto oscillatory NCCs of conscious experience reviewed so far. This will not be exhaustive, to avoid repetition, but rather an exercise and illustration of the core concepts. For instance, it immediately becomes clear that many of the previously discussed empirical findings may fall in the ‘prerequisites’ category (Busch et al., 2009; Ergenoglu et al., 2004; Hanslmayr et al., 2007; Lange, Keil, Schnitzler, van Dijk, & Weisz, 2014; Romei et al., 2008; van Dijk et al., 2008). After all, any neuronal mechanism that occurs *prior* to a conscious experience can by definition not be a neural substrate or neural consequence of a conscious experience (de Graaf et al., 2012). In other words, beta, gamma, but most notably alpha power, phase, and coherence that occur before or at the moment of stimulus presentation, are either not required for conscious experience, or are prerequisites for it. They are empirical neural correlates, they can cause a conscious experience (later), but they cannot underlie the conscious experience itself (i.e. they are not substrates). This is because when the stimulus appears on a computer screen, there is not *immediately* a conscious experience of that stimulus. The visual information still needs to affect the retina, undergo rudimentary processing along several subcortical stations, reach primary visual cortex to be processed further, and only from that point onwards could one reasonably start to wonder whether neural processing is or is not a substrate of a conscious experience (e.g. Silvanto et al., 2008).

On the one hand, one might argue that oscillatory phase at stimulus onset is reflective of oscillatory phase in the near-future. If one speculates that relevant visual processing occurs in primary visual cortex around 100 ms after stimulus onset (e.g. de Graaf, Koivisto, Jacobs, & Sack, 2014), then alpha oscillations should actually be at the same phase when the information reaches the cortex, as was measured at stimulus onset. Thus, *indirectly*, peri-stimulus oscillatory correlates might still provide clues on neural substrates of consciousness. On the other hand, it is unclear at the moment to what extent the presentation of the stimulus itself changes ‘ongoing’ oscillations, for instance causing an oscillatory phase-reset. Such considerations make it all the more important that some studies try to bypass certain sensory processing stages, for instance by magnetically

stimulating occipital cortex directly. It is thus non-trivial that similar alpha power/phase effects on conscious experience (phosphene perception) were found in these studies (Dugué et al., 2011; Romei et al., 2008a).

In Figure 4 a tentative model provides a *hypothetical* example of how *prerequisites* and *substrates* of consciousness may be related to different oscillatory correlates. We explained that a stimulus presented near sensory threshold may cause conscious experience depending on the brain state at the moment of its appearance. It might be that when power and phase of oscillatory activity fall under favorable circumstances (e.g. local alpha power in sensory – visual – areas has a momentary state below a particular threshold), they constitute (some of the) *prerequisites* necessary for a stimulus to become conscious. At this stage conscious experience is not yet achieved. Only when other mechanisms are engaged (e.g. long-range beta or gamma synchronization between low and high-order areas) conscious experience arises. The big challenge is to determine which of these additional processes are *substrates* of conscious vision.



**Figure 4:** A proof-of-concept illustration of how different oscillatory correlates could constitute prerequisites versus substrates. When a stimulus is presented at sensory threshold (a), it causes conscious experience (c) only if alpha power is sufficiently low (*prerequisite* in this example). Other oscillatory correlates (long-range synchronization in gamma or beta band in this example) can then arise, underlying the experience itself (*substrates*).

Other empirical results presented here could potentially be reconsidered similarly. Gamma power, for example, was a long-standing candidate NCC. But there are recent findings that suggest that gamma oscillatory power is not, in the end, absolutely and always necessary nor sufficient for conscious experience (Luo et al., 2009). Formally speaking, that would mean gamma oscillatory power is not a universal prerequisite. But it could also be that it is required for some conscious experiences, such as coherent percepts that require binding of different visual features, and as such a prerequisite for specific experience and what one might call a precursor of conscious perception. Future studies should illuminate this issue, also clearly separating oscillatory gamma power from gamma-band coherence across regions.

The same could be said for beta-band oscillations. We did not cover many studies focusing on beta, but beta-band coherence still seems to be a candidate NCC. Beta-band responses to conscious perception seem to occur on a temporal scale that is consistent with conscious visual experiences, thus deserving further study. At the same time, one of the two main studies discussed that related beta-band oscillations to conscious perception actually employed the attentional blink paradigm (Gross et al., 2004). Which leads us to arguably the largest confounder in NCC research: attention.

### 2.6.3 Attention, consciousness, oscillations: blurred lines

Consciousness rarely seems to occur without attention, leading many researchers to argue that attention and consciousness are inextricably connected, if not the same process (Chun & Wolfe, 2000; O'Regan & Noe, 2001; Posner, 1994). Yet, others have argued that they are distinct phenomena, with distinct functions and neuronal mechanisms (Dehaene et al., 2006; Iwasaki, 1993; Koch & Tsuchiya, 2007; Lamme, 2003). Some recent neurophysiological evidence showed that a dissociation is not completely established (Chica & Bartolomeo, 2012), yet there are empirical demonstrations that reveal separated or even opposite effects of attention manipulations versus stimulus visibility (i.e. conscious perception) manipulations (van Boxtel, Tsuchiya, & Koch, 2010; Watanabe et al., 2011).

The finer points of this ongoing discussion are beyond the scope of this review, but it is important to realize that many empirical correlates reviewed here can, in fact, also be interpreted as correlates of attention, rather than consciousness. Or at least, attention as a confounder can only rarely be ruled out. Many ON-OFF paradigms involve visual detection tasks, which could be said to either capture attentional efficacy, or conscious access. We saw that alpha power predicts conscious visual experience, but alpha power also indexes performance on explicit attention tasks (Thut, Nietzel, Brandt, & Pascual-Leone, 2006). One example paradigm that demonstrates the entanglement of attention, conscious

experience, and their relation to oscillations, is the attentional blink paradigm.

As we saw above, alpha oscillations play a prominent (yet not fully clear) role in attention and consciousness. In most attentional blink studies, the presentation rate for targets and distracters is approximately 10 Hz. Recent work has addressed the idea that the rhythmic stream of inputs in the attentional blink paradigm actually entrains alpha oscillations (Moratti, Clementz, Gao, Ortiz, & Keil, 2007). This phase-locking appears to result in visual stimulus presentation coinciding with troughs of EEG-measured parieto-occipital alpha oscillations (Hanslmayr, Gross, Klimesch, & Shapiro, 2011). Moreover, pre-stimulus alpha phase at the onset of T1 predicts whether or not T2 will be detected (Zauner et al., 2012). These findings are in line with another study which suggests that, under strict temporal constraints, the processing of the pre-target distracter stream enhances phase locking of the alpha oscillation, which predicts lower T2 detection (Petro & Keil, 2015). Lastly, the notion that oscillatory entrainment is somehow involved in attentional blink suppression is supported by the fact that introducing temporal discontinuities in the RSVP stream around presentation of T1/T2 reduces the attentional blink effect (Martin, Enns, & Shapiro, 2011).

## 2.7 CONCLUSION

To chart the exact cascade of neurocognitive events leading from visual inputs to eventual button presses, with attention and a conscious experience somewhere along the way, is still an enormous challenge. It is clear that oscillatory mechanisms are part of this process, but even when focusing on the visual modality, there is no single oscillatory mechanism that emerges as the core candidate for conscious processing. The tools to tease apart the role of various reported oscillatory correlates of consciousness are still evolving, with sophisticated developments in tACS entrainment procedures as a recent methodological highlight. Different parameters of oscillatory activity, frequency, power, phase, and coherence, should be evaluated with these new tools, to eventually distinguish their roles and contributions.

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# 3

## Relating alpha power modulations to competing visuospatial attention theories

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## ABSTRACT

Visuospatial attention theories often propose hemispheric asymmetries underlying the control of attention. In general support of these theories, previous EEG/MEG studies have shown that spatial attention is associated with hemispheric modulation of posterior alpha power (gating by inhibition). However, since measures of alpha power are typically expressed as lateralization scores, or collapsed across left and right attention shifts, the individual hemispheric contribution to the attentional control mechanism remains unclear. This is, however, the most crucial and decisive aspect in which the currently competing attention theories continue to disagree. To resolve this long-standing conflict, we derived predictions regarding alpha power modulations from Heilman's hemispatial theory and Kinsbourne's interhemispheric competition theory and tested them empirically in an EEG experiment. We used an attention paradigm capable of isolating alpha power modulation in two attentional states, namely attentional bias in a neutral cue condition and spatial orienting following directional cues. Differential alpha modulations were found for both hemispheres across conditions. When anticipating peripheral visual targets without preceding directional cues (neutral condition), posterior alpha power in the left hemisphere was generally lower and more strongly modulated than in the right hemisphere, in line with the interhemispheric competition theory. Intriguingly, however, while alpha power in the right hemisphere was modulated by both, cue-directed leftward and rightward attention shifts, the left hemisphere only showed modulations by rightward shifts of spatial attention, in line with the hemispatial theory. This suggests that the two theories may not be mutually exclusive, but rather apply to different attentional states.

## 3.1 INTRODUCTION

*Visuospatial attention* allows selection and suppression of incoming visual information. Current functional-anatomical models agree on the importance of fronto-parietal networks in attentional control and emphasize hemispheric asymmetries in their functional organization. However, there is long-standing disagreement regarding the exact role of each hemisphere in attention and their interactions. This becomes particularly apparent in the divergent attempts to explain why attention deficits following unilateral brain damage (hemineglect) are commonly more severe and prevalent after right hemispheric damage (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005).

The '*hemispatial*' theory states that the right hemisphere is involved when attending to the left and right hemifields, whereas the left hemisphere is only involved when attending to the right hemifield (Heilman & Van Den Abell,

1980). Hemineglect would thus originate from a loss of function, with right hemisphere damage causing attention deficits in the left hemifield because the intact left hemisphere is restricted to the right hemifield, whereas left hemisphere damage can be compensated for because the intact right hemisphere encompasses both hemifields. In some sense, this functional asymmetry can be considered a right hemispheric dominance in attention.

In contrast, the '*interhemispheric competition*' theory proposes that competitive interactions between hemispheres lead to prioritization of one hemifield over the other (Kinsbourne, 1977). Each hemisphere exerts a bias toward the contralateral hemifield and they mutually inhibit each other via transcallosal connections. An often overlooked aspect of this theory is that the rightward bias of the left hemisphere is argued to be stronger than the leftward bias of the right hemisphere. Consequently, hemineglect should not be described as a loss of function but it rather reflects severely biased competition between hemispheres. Right hemisphere damage leaves the stronger rightward bias of the left hemisphere unopposed forcing attention away from the left hemifield, whereas left hemisphere damage only exposes the relatively mild leftward bias of the right hemisphere. This hemispheric asymmetry can be considered a left hemispheric dominance in attention.

A separate line of research has focused on the role of posterior oscillatory brain activity within the alpha range (7-13 Hz) either using tasks explicitly requiring voluntary shifts of spatial attention (Dombrowe & Hilgetag, 2014; Rihs, Michel, & Thut, 2007; Sauseng et al., 2005; Worden, Foxe, Wang, & Simpson, 2000; Yamagishi, Goda, Callan, Anderson, & Kawato, 2005) or implicitly assessing attentional processes by probing variations in perceptual performance (Hanslmayr et al., 2007; Lange, Oostenveld, & Fries, 2013; van Dijk, Schoffelen, Oostenveld, & Jensen, 2008). Voluntary shifts of attention to one hemifield have generally been found to be associated with alpha power lateralization, typically resulting from contralateral decreases and/or ipsilateral increases of alpha power relative to the locus of spatial attention (Gould, Rushworth, & Nobre, 2011; Händel, Haarmeier, & Jensen, 2011; Kelly, Lalor, Reilly, & Foxe, 2006; Rihs et al., 2007; Rihs, Michel, & Thut, 2009; Sauseng et al., 2005; Thut, Nietzel, Brandt, & Pascual-Leone, 2006; Worden et al., 2000; Yamagishi et al., 2003, 2005). Similarly, alpha power prior to the presentation of visual stimuli is predictive of general task performance (Händel et al., 2011; Hanslmayr et al., 2007; Thut et al., 2006; van Dijk et al., 2008), but has also been linked to spatially-specific attentional biases that spontaneously occur in visual tasks (Boncompagni, Villena-González, Cosmelli, & López, 2016).

Alpha power can thus serve as an index of attentional control processes. Importantly, alpha oscillations are widely thought to reflect inhibitory processes, and alpha power lateralization may thus be interpreted as a mechanism that facilitates stimulus processing by i) enhancing responses at attended locations

(Hopfinger, Buonocore, & Mangun, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999) and ii) suppressing potential distractors at unattended locations (Jensen & Mazaheri, 2010; Klimesch, Sauseng, & Hanslmayr, 2007).

Based on the two aforementioned models of attentional control, diverging predictions regarding alpha power modulation can be derived: according to the hemispatial theory, attention allocation to the left visual field involves only the right hemisphere; so only a right hemispheric alpha power decrease is expected. In attention allocation to the right visual field both hemispheres are involved, suggesting bilateral alpha power modulation with a left hemispheric decrease and a right hemispheric increase. According to the interhemispheric competition theory, the balance between hemispheres determines the locus of attention, with the left hemisphere generating a stronger rightward bias as compared to the leftward bias generated by the right hemisphere. This left hemispheric dominance could be observable in different levels of alpha power between left and right hemispheres. Additionally, competitive interactions between hemispheres are predicted to occur during shifts of attention, implying that attention allocation toward either hemifield leads to bilateral alpha power modulation with a contralateral alpha power decrease and an ipsilateral alpha power increase. The recurring observation in the literature of alpha power lateralization in some sense matches key aspects of this interhemispheric competition theory, but this correspondence might be misleading, as it will be shown below.

The vast majority of previous studies has focused on alpha power lateralization indices, thus quantifying the difference in alpha power between the left and right hemispheres (Händel et al., 2011; Kelly et al., 2006; Rihs et al., 2009; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000), or directly contrasted leftward and rightward attentional shifts, thereby ignoring hemifield-specific contributions by collapsing the assumed contralateral decreases and ipsilateral increases (Marshall, O'Shea, Jensen, & Bergmann, 2015). The observed lateralization might arise from contralateral decreases, ipsilateral increases or both (Kelly et al., 2006; Rihs et al., 2009; Sauseng et al., 2005; Worden et al., 2000). Therefore, this collapsing of data across hemifields and/or hemispheres fails to reveal potentially important hemispheric asymmetries. Moreover, it is common practice to reference alpha power during attention shifts to alpha power prior to attention shifts (Ikkai, Dandekar, & Curtis, 2016; Kelly et al., 2006; van Diepen, Miller, Mazaheri, & Geng, 2016; Wildegger, van Ede, Woolrich, Gillebert, & Nobre, 2017). However, this procedure may fail to control for other task-related preparatory activities. The inclusion of a baseline condition (neutral cues) that accounts for such effects may allow isolating alpha power changes specific to attention shifts without such confounders.

We set out to relate alpha power modulations to Kinsbourne's interhemispheric competition theory and Heilman's hemispatial theory. Surprisingly, despite the well-established relation between alpha power and

attention, such a full characterization of alpha power modulations across hemispheres and attentional states (bias at “baseline” versus shifts of attention) is still lacking. We here report alpha power changes during a spatial orienting paradigm for each hemisphere and three attention conditions separately. We first explored the dynamics of posterior alpha power in a neutral cue condition that does not require any shifts of attention (baseline), thus relating to the concept of attentional bias. We then assessed the magnitude of alpha power up- and down-regulation for leftward and rightward attention shifts relative to that baseline. Critically, this allowed us to control for task effects that are shared by directional and non-directional cues, normally not identifiable when comparing to a pre-cue baseline. By using this approach, we were able to directly test the key predictions derived from competing models of attentional control in two attentional states.

## 3.2 MATERIAL AND METHODS

### 3.2.1 Overall study design

The results presented here are part of a larger project involving functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS) and electroencephalography (EEG). The project included one fMRI session for frontal eye fields (FEFs) localization and three TMS sessions counterbalanced in a within-subjects design. TMS studies commonly involve a placebo condition: the data reported here stem from EEG sessions that were preceded by 40 seconds of offline placebo TMS with no direct neural effects.

### 3.2.2 Participants

Twenty-seven healthy participants took part in the experiment (8 men, M age: 21.9, SD: 2.5). All of them were right-handed, had normal or corrected-to-normal vision and did not report any history of neurological or psychiatric disorders. Before each session participants provided written informed consent and filled out a screening form for TMS contraindications. The study was approved by the Ethics Review Committee Psychology and Neuroscience at Maastricht University.

### 3.2.3 Procedure

Before starting the task, participants performed a short practice session identical to the real task, except that they received feedback on their performance. In this practice session we ensured that performance was sufficiently accurate and fast, and modulated by presented symbolic cues (see below). Next, an EEG cap was prepared using electroconductive paste (MedCat, OneStep ClearGel,

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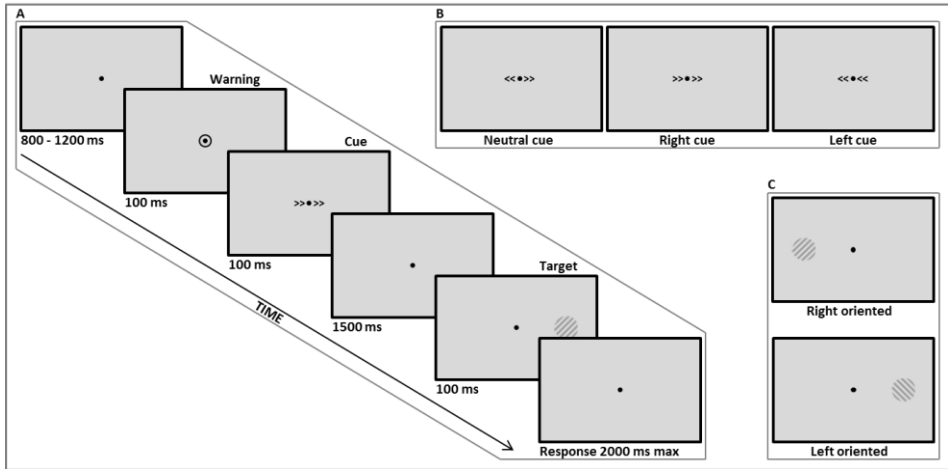
Klazienaveen, The Netherlands). Participants received fMRI-guided placebo TMS over either the left or the right FEF using a continuous theta burst stimulation protocol (50-Hz triplets were delivered 5 times a second for 40 seconds, 600 pulses in total). TMS was delivered with a purpose-built placebo TMS coil (MC-P-B70, MagVenture, Farum, Denmark) with strong attenuation of the magnetic field so that no effective stimulation occurred. The stimulation site was counterbalanced across participants, targeting the left FEF in half of the cases and the right FEF in the other half. After the stimulation, participants were seated in front of a computer screen with their head supported by a chin rest at a viewing distance of 57 cm. As already indicated above, data were recorded without neuromodulation, and without any placebo TMS during task execution. There was only a 40-second placebo TMS protocol at the start of the experimental session, after which all TMS equipment was removed.

#### 3.2.4 Task and stimuli

During the EEG measurements, participants performed a spatial orienting task consisting of 504 trials divided in 6 blocks composed of 84 trials each (plus 4 warm-up trials included at the beginning of each block). The task took around 40 mins to complete. Visual stimuli were presented on a gamma corrected 24-inch monitor (Iiyama ProLite B2481HS-B1, Iiyama, Japan) using a 1920 x 1080 (60Hz) mode. The software Presentation (version 19.0, NeuroBehavioral System, Albany, CA) was used to display visual stimuli and record behavioral responses.

Symbolic cues were used to direct covert shifts of visual attention in space (Posner, 1980). During the task, a black dot was constantly shown at the center of the screen (•). The start of a trial was announced by a circle presented around the central dot (◉) 100 ms before cue onset. Spatial cues consisted of two double arrowheads next to the central dot pointing leftward (<<•<<) or rightward (>>•>>), prompting participants' covert attention toward one hemifield. The neutral cue consisted of two double arrowheads pointing in opposite directions (<<•>>), providing temporal but not spatial information. The cue duration was 100 ms, after which there was an interval of 1500 ms before the appearance of the target (i.e. stimulus onset asynchrony [SOA] 1600 ms). Target stimuli were Gabor patches (spatial frequency = 1.5 cycles per degree, envelope standard deviations = 0.75°, Michelson contrast = 60%, randomly tilted 45° to the left or right) presented for 100 ms at 7° eccentricity either on the left or right side of the fixation point. Participants were instructed to identify the target orientation independently of its location, and respond as quickly and accurately as possible. They responded using a computer keyboard, pressing Numpad1 (left orientation) using the right index finger or Numpad2 (right orientation) using the right middle finger. The button press ended the trial; onset of the next trial followed after either 800, 1000, or 1200 ms.

Trials were defined as *valid* when cue direction and target position were congruent (e.g. cue pointing to the right, target appearing on the right side of the fixation point), *neutral* in the case of a neutral cue, and *invalid* when cue direction and target position were incongruent (e.g. cue pointing to the right, target appearing on the left side of the fixation point). Figure 1 shows an example of a trial. The combination of the three types of cue (left, right, and neutral) and the two positions of the target (left, right) resulted in six conditions. The presentation frequency of valid, neutral and invalid trials was not equally balanced across conditions but had a ratio of 4:2:1 respectively, to ensure that symbolic cues were sufficiently informative.



**Figure 1:** A) Representation of a possible trial and the time intervals between trial events; in this example (a valid trial) the cue prompts attention toward the right hemifield and the target appears at the same location. B) Neutral and spatial (left and right) cues. C) Possible target locations (left, right) and orientations (right oriented, left oriented).

### 3.2.5 EEG Recording and pre-processing

#### 3.2.5.1 Recording

Brain activity was recorded using a 64-channel EEG system (EasyCap, Brain Products GmbH, Munich, Germany) composed of sintered Ag/AgCl TMS-compatible passive electrodes placed over the scalp according to the 10/10 international system. Electro-oculography (EOG) was used to record eye artifacts. EOG electrodes measuring horizontal eye movements were positioned on the outer canthi of the left and right eyes, whereas vertical eye movements were identified from two electrodes, one placed below the left eye and Fp1. FCz was used as a reference electrode and AFz as a ground electrode. During the recording the signal was amplified by using 2 amplifiers of 32 channels each

(Brain Products GmbH, Munich, Germany), digitized using a sampling rate of 500 Hz, and stored on a hard disk using the software BrainVision Recorder (BrainProducts GmbH, Munich, Germany). The impedance of the signal was kept below 5 K $\Omega$  and online low-pass (100 Hz), high-pass (0.53 Hz) and notch (50 Hz) filters were used.

### *3.2.5.2 Pre-processing*

EEG data were preprocessed and analyzed using both custom-written Matlab scripts (The MathWorks Inc., Natick, USA, version 2014a) and the FieldTrip toolbox version 2014 (Oostenveld, Fries, Maris, & Schoffelen, 2011). The signal was epoched in segments of 2.9 sec starting at 0.8 sec before and ending at 2.1 sec after the onset of the cue (time 0). After this process a low-pass filter at 60 Hz was applied. The filtered EEG activity was offline re-referenced to the mean activity of all EEG channels. For the identification of “eye movement-contaminated” trials we used two approaches: taking advantage of the eye channels we firstly performed a visual inspection of each trial and removed the ones containing blinks and/or saccades. This step was done to assure that within the time window of our interest (cue-target interval [0 - 1.6 s]) no eye movements occurred. Secondly, an independent component analysis (ICA) was used to identify other types of artifact (e.g. muscle movements, amplifier saturation) and to detect the remaining eye movement artifacts occurred outside of the time period included in the previous inspection [-0.8 - 0 s, 1.6 - 2.1 s] (Jung et al., 2000). The proportion of trials not included in the subsequent analyses was 17.1 % on average. This proportion was similar across conditions.

### 3.2.6 EEG analysis

A time-frequency analysis was performed using the Morlet wavelet approach. The sliding wavelet had a constant length of 300 ms, whereas its number of cycles varied in a frequency-dependent manner and was obtained by multiplying the frequency of interest by the length of the wavelet in seconds (i.e.  $n^{\circ}$  cycles = frequency x 0.3 sec). The wavelet moved along frequencies in steps of 0.5 Hz from 5 Hz to 30 Hz and along time points in steps of 50 ms throughout the entire epoch [-0.8 – 2.1 s]. Given that our analyses described below exclusively focused on a narrow frequency band (alpha), this approach may seem unnecessarily convoluted. The primary motivation for this was to ensure comparability of the present study with planned analyses of our TMS conditions (not reported here) which will ultimately be compared to a TMS/MEG study by Marshall et al. (2015) who used a similar approach.



### 3.2.7 Statistical analysis of behavioral data

Individual mean reaction times (RTs) were based on trials with correct responses, and analyzed in a 3 X 2 repeated-measures analysis of variance (ANOVA) with Cue Validity (valid, neutral and invalid) and Hemifield (left and right) as within-subject factors. Greenhouse-Geisser correction was applied to compensate the violation of assumed sphericity for the factor Cue Validity. Follow-up t-tests were then performed to investigate RT differences between valid trials and neutral trials, and between invalid trials and neutral trials.

### 3.2.8 Statistical analysis of EEG data

Data of one participant were not included in the analyses due to technical problems during data acquisition, and data of two participants were excluded from the analyses due to statistical outliers in the within-subject differences ( $> 1.5$  times the interquartile range away from the 25<sup>th</sup> or the 75<sup>th</sup> percentile of the samples) either in the neutral or in the spatial cue conditions. EEG analysis was performed on data from the remaining 24 participants. Since we were interested in the modulation of posterior alpha-band activity in a specific time interval, the statistical analysis was performed on subsets of channels, frequencies and time points. The alpha power estimation was obtained for right parietal cortex (PO4, PO8, P4, P6, P8) and left parietal cortex (PO3, PO7, P3, P5, P7) separately, by averaging the time-frequency analysis results over channels and alpha-frequency bins (7-13 Hz).

We performed three sets of analyses that are outlined below. For neutral cue trials, we were interested in general alpha power differences between hemispheres in the absence of attention shifts, but also in the dynamics of alpha power changes during the cue-target interval to illustrate the need for this control condition when isolating orienting-specific processes. For directional cue trials, we focused on the critical period of the cue-target interval when alpha power modulation related to shifts of attention is expected to occur. Lastly, we performed two conventional analyses that do not take advantage of a neutral cue condition, mainly for the purpose of comparison but also to emphasize the added value of our methodology.

#### *3.2.8.1 Neutral cue*

We first evaluated whether there was an overall difference in hemispheric engagement, over the whole epoch, as indexed by an absolute alpha power difference between hemispheres. Since this analysis involves comparisons of *raw* alpha power, as opposed to baseline-corrected alpha power as below, we performed a logarithmic transformation of alpha power at the single-epoch level (Smulders, ten Oever, Donkers, Quaedflieg, & van de Ven, 2018), which has

previously been shown to sufficiently counter variability of raw alpha power over trials within participants (Haegens, Cousijn, Wallis, Harrison, & Nobre, 2014; Smulders et al., 2018) and between participants (Haegens et al., 2014; Klimesch, 1999). Though primarily interested in an overall alpha power difference between hemispheres (collapsed over the epoch [-0.65 – 1.45 s], compared in a paired samples t-test), we also checked whether this difference changed within the epoch. For this, we compared alpha power for each time point of the epoch using Monte Carlo simulations to estimate p-values with 10,000 randomizations. Multiple comparison correction was implemented at cluster level with an alpha of 0.05, and by controlling the family-wise error rate using the cluster statistics also at an alpha of 0.05 (Maris, 2012).

Secondly, we assessed for each hemisphere how it responded to alerting cues. To test this, we measured whether neutral cues modulated alpha power. We now baseline-corrected (relative change, baseline period: [-0.65 - -0.25 s]) the (not log-transformed) raw alpha power averaged over trials. Baseline-corrected values were then tested against 0, separately per time point and cluster-threshold corrected for multiple corrections as above. We then collapsed the data over time [0.4 – 1.45 s] and tested left and right hemispheres against each other using a paired samples t-test.

### 3.2.8.2 *Spatial cues*

To test whether the magnitude of alpha power was significantly different between neutral and spatial cues we normalized (i.e. divided) every time-point of raw alpha power (not log-transformed) in response to spatial cues by the corresponding time-point of raw alpha power obtained from the neutral cue (no attentional shifts). We then averaged time points within the cue-target interval, when we expected alpha power modulation related to the shift of attention. To prevent confounding of the alpha power estimate with the event-related activity generated by the presentation of the cue, the epoch of interest started after the visual processing of the cue and ended 150 ms before the target onset [0.4 – 1.45 s]. The results were tested against 1 using a one-tailed paired samples t-test, based on clear a priori hypotheses about the expected directionality of alpha power modulation in these analyses. This computation allowed us to reveal alpha power changes related to left and right attentional shifts compared to no attentional shifts, separately per hemisphere. Lastly, we computed a 2 x 2 ANOVA with Hemifield (contralateral, ipsilateral) and Hemisphere (left, right) as within-subject factors and, to formally quantify the absolute magnitude difference between these conditions, two paired samples t-tests for both hemispheres.

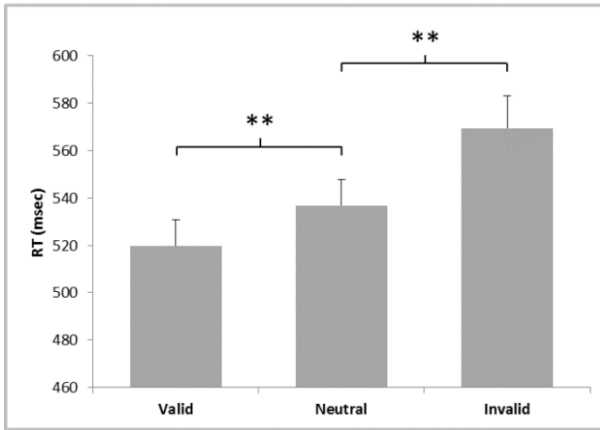
### 3.2.8.3 Baseline correction and Attentional Modulation Index approaches

To better understand the benefits of normalizing the data by the neutral cue, we also performed two conventional analysis approaches of the directional cue conditions. First, we used standard baseline correction of the raw alpha power (absolute, baseline period: [-0.65 - -0.25 s]) to check how alpha power changed during the cue-target interval as compared to the pre-cue period. The levels of alpha power for left and right hemispheres were then tested against 0 using paired samples t-tests. Second, we computed an attentional modulation index (AMI) by subtracting the raw alpha power related to right shifts of attention from the alpha power related to left shifts of attention and then dividing by their average. In principle, the AMI should reveal the traditional pattern of ipsilateral alpha power increase and contralateral decrease and we therefore tested alpha power for the left and right hemispheres against 0 using paired samples t-tests.

## 3.3 RESULTS

### 3.3.1 Behavioral

We first evaluated whether attentional cues (valid, invalid, neutral) modulated reaction times to targets presented to either Hemifield (left, right). The repeated-measures ANOVA showed significant main effects of Cue ( $F_{(1,185,27,260)} = 45.627$ ,  $p < .001$ ) and Hemifield ( $F_{(1,23)} = 7.110$ ,  $p < .05$ ), and a non-significant Cue X Hemifield interaction ( $F_{(2,46)} = 3.096$ ,  $p > .05$ ). The main effect of Cue was further investigated with follow-up t-tests showing faster RTs for valid trials ( $t_{(23)} = -6.398$ ,  $p < .001$ ) and slower RTs for invalid trials ( $t_{(23)} = 5.963$ ,  $p < .001$ ) both compared to neutral trials (see Fig. 2). The presence of attentional benefits and attentional costs in our reaction time data demonstrates that participants covertly shifted their attention toward the cued locations. This was expected based on our previous results (Duecker, Formisano, & Sack, 2013), but not trivial given the much longer cue-target SOA (1600 ms) we used compared to our previous implementations (600 ms). The replication of these behavioral results with the current parameters was a crucial prerequisite for the EEG analysis, allowing us to investigate alpha power modulations in the longer cue-target interval in response to attentional shifts. The main effect of Hemifield resulted from faster RTs for targets presented in the right hemifield, probably because participants responded with the right hand, leading to the Simon effect (Simon & Rudell, 1967).



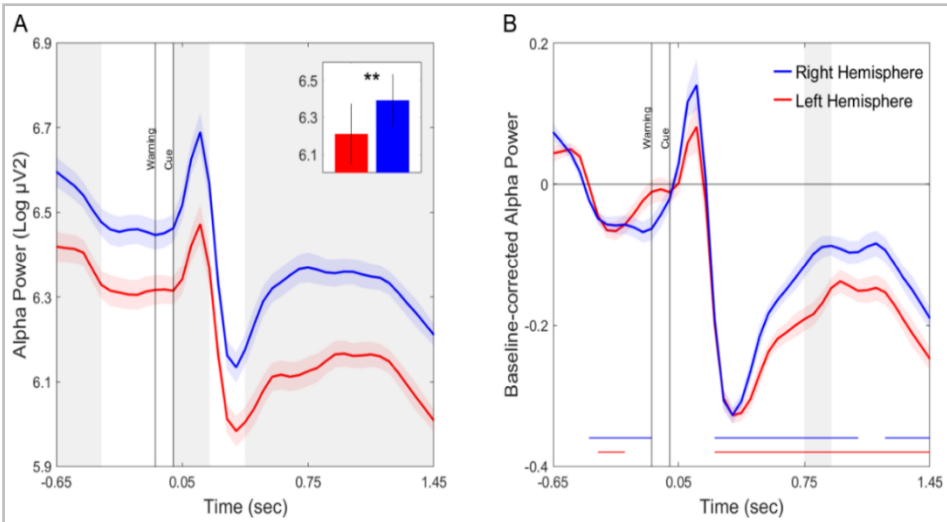
**Figure 2:** Reaction times (RTs) for valid, neutral and invalid trials. Differences between bars marked with two asterisks are statistically significant ( $p < .001$ ); error bars represent SEM across subjects.

### 3.3.2 EEG

#### 3.3.2.1 Neutral cue

Logarithmically transformed alpha power in the left hemisphere was overall (collapsed over the entire epoch) lower than in the right hemisphere ( $t_{(23)} = 2.886$ ,  $p < .01$ ; Fig. 3A, top right panel). Over the course of the epoch, we found three clusters with statistically significant differences (cluster statistics, early to late: 14.055,  $p < .03$ , 12.430,  $p < .05$ , 68.317,  $p < .01$ ; Fig. 3A).

To understand how much the presentation of a neutral cue (no attentional shifts) influenced alpha power in each hemisphere, baseline-corrected alpha power was tested against 0 for the left and the right hemispheres separately. In both hemispheres alpha power decreased after the presentation of the cue (cluster statistics, early to late for the left hemisphere: -12.8468,  $p < .05$ , -166.664,  $p < .0001$  and for the right hemisphere: -22.8451,  $p < 0.03$ , -82.8825,  $p < .0001$ , -22.1266,  $p < .03$ ; Fig. 3B). After the presentation of the neutral cue the left hemisphere showed a greater negative alpha power modulation compared to the right hemisphere (cluster statistics, over time: -10.1301,  $p < 0.05$ ; averaged over time [0.4 – 1.45 s]:  $t_{(23)} = -2.441$ ,  $p < .03$ , Fig. 3B). This might suggest that the left hemisphere more successfully maintains a state of alertness after an alerting cue, thus creating an attentional bias at baseline.



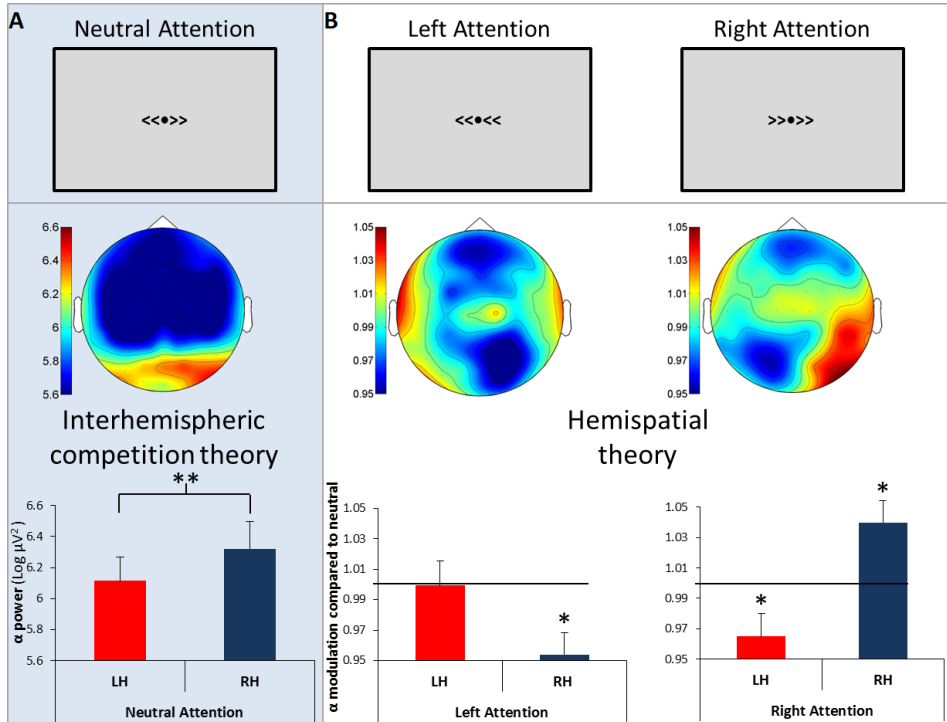
**Figure 3:** A) Time evolution of log-transformed alpha power for the left (red line) and right (blue line) hemispheres. Light red and light blue areas represent SEM across subjects. Light grey areas represent the time windows in which the two time courses significantly differ from each other ( $p < 0.05$ , cluster correction). The two bars in the top right panel represent alpha power levels averaged over time throughout the entire epoch  $[-0.65 - 1.45]$ ; the two asterisks represent a significant difference between bars ( $p < .01$ ); error bars represent SEM across subjects. B) Time evolution of baseline-corrected (baseline period:  $[-0.65 - -0.25]$ ) alpha power for the left (red line) and right (blue line) hemispheres. Lines in the baseline period are above and below 0, leading to an average value of 0. Light red and light blue areas represent SEM across subjects. The light grey area represents the time window in which the two time courses significantly differ from each other ( $p < 0.05$ , cluster correction). Red and blue lines at the bottom of the figure represent the time windows in which the two time courses significantly differ from 0 ( $p < 0.05$ , cluster correction).

### 3.3.2.2 Spatial cues

To reveal the magnitude and direction of spatial cue-induced alpha power changes separately for the left and right hemispheres, we normalized (i.e. divided) the spatial cues alpha power levels to the alpha power level obtained in the neutral cue condition. This means the results *isolate* the spatial orienting component in the alpha modulation, having controlled for the temporal and alerting effects of cues. Topoplots and bars shown in Figure 4 B depict normalized alpha power averaged across time points from 0.4 sec to 1.45 sec after the presentation of the cue.

In the right hemisphere alpha power increased ( $t_{(23)} = 2.005$ ,  $p < .03$ ) when attention was deployed to the ipsilateral side (right cue condition), whereas it

decreased ( $t_{(23)} = -3.236, p < .01$ ) when attention was deployed to the contralateral side (left cue condition) in both cases compared to when attention was not deployed in visual space (neutral cue condition). In the left hemisphere alpha power was modulated differently. While it decreased when attention was deployed to the contralateral side ( $t_{(23)} = -2.286, p < .03$ ), it did not increase when attention was deployed to the ipsilateral side ( $t_{(23)} = -0.047, p > .51$ ).

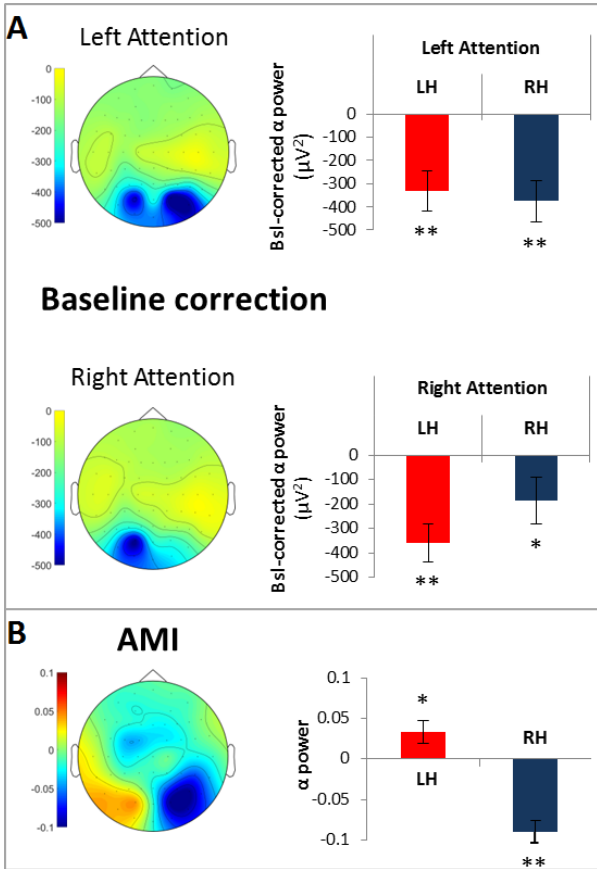


**Figure 4:** A). The alpha pattern obtained in response to a neutral cue matches the interhemispheric competition theory. The topoplot shows log-transformed alpha power in response to a neutral cue (no shifts of attention) in the time interval [0.4 – 1.45 s]. The bar graph shows the same data averaged over time for the left and right occipito-parietal electrodes. The two asterisks represent statistical significance between hemispheres. Error bars represent SEM across subjects. B). The alpha pattern obtained in response to directional cues matches the hemispatial theory. Right attention leads to a contralateral alpha decrease and an ipsilateral alpha increase. Left attention leads to a contralateral alpha decrease. The topoplots show posterior alpha power modulation in response to directional cues (left and right) as compared to the neutral cue in the time interval [0.4 – 1.45 s]. The bar graphs show the same data averaged over time for the left and right occipito-parietal electrodes. Bars marked with an asterisk are statistically different with respect to the neutral attention condition ( $p < .05$ , 1-tail t-test). Error bars represent SEM across subjects.

Complementary to the planned t-tests, we performed a 2 X 2 ANOVA to evaluate whether there was any difference in the magnitude of the obtained alpha power modulations. In line with the t-tests, the analysis showed a Hemisphere x Hemifield interaction approaching significance ( $F_{(1,23)} = 3.978$ ,  $p < .06$ ), a main effect of Hemifield ( $F_{(1,23)} = 77.654$ ,  $p < .001$ ) and no effect of Hemisphere ( $F_{(1,23)} = 1.649$ ,  $p > .21$ ). In light of the results obtained from the previous analysis we performed a further investigation of the interaction. Follow-up t-tests showed a significant difference when attention was shifted to the ipsilateral side of space between left and right hemispheres ( $t_{(23)} = -2.099$ ,  $p < .05$ ) and no difference when attention was shifted to the contralateral side of space ( $t_{(23)} = 0.731$ ,  $p > .47$ ).

### *3.3.2.3 Baseline correction and Attentional Modulation Index*

To illustrate the benefit of normalizing to a neutral cue condition, we also analysed the same data using two conventional approaches. Figure 5A depicts the alpha power level averaged across time points from 0.4 to 1.45 seconds after the presentation of the cue, obtained for the left and right attention conditions after having applied baseline correction. The topoplots and the bar graphs show that alpha power generally decreased after the presentation of the cue in both hemispheres for the left attention condition (left hemisphere:  $t_{(23)} = -4.537$ ,  $p < .001$ , right hemisphere:  $t_{(23)} = -5.038$ ,  $p < .001$ ) as well as for the right attention condition (left hemisphere:  $t_{(23)} = -5.491$ ,  $p < .001$ , right hemisphere:  $t_{(23)} = -2.293$ ,  $p < .05$ ). Importantly, no significant differences were found between hemispheres (left vs right hemisphere for the left attention condition:  $t_{(23)} = 1.218$ ,  $p > .23$ , left vs right hemisphere for the right attention condition:  $t_{(23)} = -1.613$ ,  $p > .12$ ).



**Figure 5:** Alternative normalization approaches. A) *Baseline corrected alpha power*. The topoplots show baseline corrected alpha power in response to directional cues (left and right) in the time interval [0.4 – 1.45 s], baseline period: [-0.65 – -0.25]. The bar graphs show the same data averaged over time for the left and right occipito-parietal electrodes. Error bars represent SEM across subjects. B) *Attentional modulation index (AMI)*. The topoplot shows alpha power in response to right cues subtracted from the alpha power in response to left cues (left – right attention)/(average of left and right attention) in the time interval [0.4 – 1.45 s]. The bar graphs show the same data averaged over time for the left and right occipito-parietal electrodes. Error bars represent SEM across subjects.

Figure 5B shows alpha power levels expressed as attentional modulation index, averaged across time points from 0.4 to 1.45 seconds after the presentation of the cue. As the topoplot shows, this resulted in the well-known pattern of alpha power increase in the left hemisphere and decrease in the right hemisphere compared to 0 (left hemisphere:  $t_{(23)} = 2.355, p < .03$ , right hemisphere:  $t_{(23)} = -5.995, p < .001$ ). This method is able to reveal alpha power lateralization in response to directional cues, but since data are collapsed across hemifields it does not reveal the single hemispheric contribution to these attentional processes.

### 3.4 DISCUSSION

Several theories have postulated a hemispheric asymmetry for the control of visuospatial attention (Corbetta & Shulman, 2011; Duecker & Sack, 2015; Heilman & Van Den Abell, 1980; Kinsbourne, 1977), but which theory



successfully predicts the hemispheric dynamics related to the allocation of attention is still a matter of debate. The aim of this study was to test predictions derived from the interhemispheric competition and the hemispatial theories. With EEG we recorded brain activity while participants performed an established spatial orienting paradigm (Posner, 1980). In this task, neutral cues provided temporal but not spatially-predictive information, and directional cues prompted covert shifts of visuospatial attention. For both of these attentional states, we quantified alpha power levels in each hemisphere separately and dissociated leftward and rightward shifts of attention. We found that posterior alpha power in the left hemisphere was generally lower than in the right hemisphere and more strongly modulated by neutral (alerting) cues. When isolating the alpha modulation induced by the spatial component of the directional cues specifically, i.e. the modulation induced by spatial attention shifts rather than temporal alerting, we found that the right hemisphere engaged in both leftward and rightward attention shifts, while the left hemisphere engaged in only rightward attention shifts. Below, we discuss how well these results match both the interhemispheric competition and the hemispatial theories.

### 3.4.1 Alpha modulation in the absence of spatial information supports the interhemispheric competition theory

The use of a neutral cue condition allowed us to reveal the *baseline* alpha power level, in the absence of spatial attention shifts. Our results show general alpha power differences between the two hemispheres, but also differences in their dynamics, i.e. the change of alpha power during the cue-target interval. Overall, the left hemisphere had lower alpha power compared to the right hemisphere throughout the entire epoch. This result is in line with a previous study that showed similar alpha power differences between hemispheres at rest (Çiçek, Nalçacı, & Kalaycioğlu, 2003). The authors suggested that this difference in alpha power might support a dominant role of the right hemisphere in attentional mechanisms and might be related to pseudoneglect, a leftward attentional bias normally present in healthy subjects (Benwell, Thut, Learmonth, & Harvey, 2013; Bowers & Heilman, 1980; Schenkenberg, Bradford, & Ajax, 1980). However, it has also been argued that alpha power is inversely related to cortical excitability (Klimesch et al., 2007), so that lower alpha power in the left hemisphere would instead indicate left hemispheric dominance. It is noteworthy that, according to the *interhemispheric competition* theory, left and right hemispheres generate a contralateral bias and are normally kept in balance by mutual inhibition, with the left hemisphere generating a stronger bias (Kinsbourne, 1977). The difference in alpha power we observed between hemispheres might be the electrophysiological marker of the stronger bias the left

hemisphere exerts toward the right hemifield, thus supporting the left hemispheric dominance proposed by Kinsbourne.

After the presentation of the neutral cue, a significant decrease of alpha power in both hemispheres was initially driven by the cue-evoked activity but then persisted throughout the entire cue-target interval. Since target stimuli were equally likely to appear in either hemifield in the neutral cue condition, preparation for visual processing is required in both hemifields. It is therefore likely that a bilateral hemispheric engagement takes place by an increase of cortical excitability, thus leading to an alpha activity decrease in both hemispheres. This result is in accordance with previous findings which showed that when a neutral cue is presented, alpha power decreases similarly in the left and right hemispheres (Ikkai et al., 2016). In our case this alpha power decrease was more pronounced in the left hemisphere when computing the relative change from the pre-cue period. Given that alpha power differences between hemispheres were already present prior to the cue, this result needs to be interpreted with caution, but it might reveal interesting nuances in the hemisphere-specific response to a seemingly simple neutral cue that does not convey any spatial information.

### 3.4.2 Alpha modulation specific to spatial orienting supports the hemispatial theory

By referencing alpha power of the directional cue conditions to alpha power of the neutral cue condition, in contrast to previous studies, we were able to assess orienting-related alpha modulations in both hemispheres separately. The right hemisphere showed alpha power decreases in response to left attention shifts, as shown previously (Gould et al., 2011; Sauseng et al., 2005; Thut et al., 2006), and in accordance with increased preparatory activity for the attended hemifield. In the case of attention deployed toward the right side, alpha power in the right hemisphere increased. This is in accordance with several studies that showed ipsilateral alpha power increases when attention is shifted toward one side of the visual space (Händel et al., 2011; Jensen & Mazaheri, 2010; Kelly et al., 2006; Worden et al., 2000). Since alpha oscillations have been ascribed an inhibitory function (Hummel, Andres, Altenmüller, Dichgans, & Gerloff, 2002; Klimesch et al., 2007), these results suggest that the right hemisphere has a dual role in attention shifts by facilitating the detection of visual stimuli in the contralateral hemifield (by decreasing alpha power), but also inhibiting the influence of irrelevant visual stimuli in the ipsilateral hemifield (by increasing alpha power).

The left hemisphere showed alpha power decreases in response to right attention shifts, mirroring the preparatory activity during contralateral attention shifts observed in the right hemisphere. Critically, alpha power did not increase compared to the neutral condition when shifting attention toward the left side.

The left hemisphere seems therefore to be only involved in facilitating detection of visual stimuli in the contralateral hemifield (by decreasing alpha power), but not in inhibiting irrelevant visual stimuli in the ipsilateral hemifield (absence of alpha power increase). This finding provides a novel insight into the relation between posterior alpha power modulation and attention allocation, showing orienting-related asymmetries not identifiable with attention modulation indexes commonly used.

In sum, the asymmetrical pattern of alpha power modulations observed after directional cues supports a right hemispheric dominance as proposed by the *hemispatial* theory of attention (Heilman & Van Den Abell, 1980), which postulates that the right hemisphere is engaged when shifting attention both toward left and right visual hemifields, but the left hemisphere only in shifting attention toward the contralateral hemifield. Importantly, the lack of alpha power increase in the left hemisphere in response to leftward shifts of attention is in conflict with the interhemispheric competition theory of attention because it postulates an engagement of both hemispheres when shifting attention to either visual hemifield, therefore predicting bilateral alpha power modulation after directional cues. The observed hemispheric asymmetries thus have direct implications for these competing theories of attentional control. Moreover, they also refine our understanding of the functional role of each hemisphere during attention shifts by separating selection and suppression of incoming sensory stimuli thereby clarifying what “involvement” of a hemisphere means.

Finally, in the conditions in which alpha power was modulated in response to attention shifts (in the right hemisphere by left and right shifts, in the left hemisphere only by right shifts) the magnitude of change did not differ between hemispheres nor hemifields. This result suggests that when a hemisphere is engaged in shifting attention, its level of engagement is comparable to the other hemisphere, independently of whether it enhances or inhibits stimulus detection. This finding seems to be in contrast with what Ikkai et al. (2016) reported, namely that contralateral attention shifts resulted in greater alpha modulation in the left than in the right hemisphere. They compared alpha modulation of directional cues to a pre-cue period, rather than the neutral cue alpha modulation. Possibly, our approach could reveal these new patterns of hemispheric involvement because it explicitly takes into account task effects shared by directional and non-directional cues.

### 3.4.3 Interpretation of the results in the context of a recent functional-anatomical model

The coexistence of the hemispatial and interhemispheric competition theories was previously proposed in the *hybrid model* of attentional control (Duecker & Sack, 2015). Based on brain stimulation studies, it was argued that distinct

hemispheric asymmetries exist in the dorsal attention network. Specifically, the hemispatial theory received strong support by TMS studies targeting frontal regions, whereas the interhemispheric theory could account for results of TMS studies targeting parietal regions. Instead of this spatial separation, our findings demonstrate distinct hemispheric asymmetries within parietal cortex depending on the attentional state. Given prior studies showing that attention shifts elicit fronto-parietal coupling within the DAN (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Buschman & Miller, 2007; Ozaki, 2011; Vossel, Weidner, Driver, Friston, & Fink, 2012) with a frontal-to-parietal directionality (Bressler et al., 2008; Ozaki, 2011; Vossel et al., 2012), it seems plausible that the pattern of alpha power modulation observed in parietal cortex is instantiated by top-down signals from frontal cortex. The present findings thus further inform this functional-anatomical model of attention control and highlight the importance of investigating the neurophysiological correlates of distinct attentional states within the dorsal attention network.

#### 3.4.4 Further considerations

While the inclusion of a neutral cue has been widely used in behavioral studies (see Chica, Martín-Arévalo, Botta, & Lupiáñez, 2014 for a review), a key novelty of the present study is to combine it with electrophysiology, allowing the isolation of orienting-specific alpha power modulations during the cue-target interval for each hemisphere and cue direction separately. Neutral cues elicit many non-directional attention responses, e.g. alerting, arousal, temporal attention, which are thus controlled for in the analyses of alpha responses to directional cues. But one challenge for future studies is to establish what participants actually do during the cue-target interval in the neutral cue condition. They might maintain central fixation without any change in attention, but they might also broaden their focus, divide attention, alternate between hemifields, or even randomly choose a hemifield based on the recent history of trials. None of these task strategies were encouraged by our instructions or rewarded by task progression. Moreover, none of them should systematically affect or confound the current results. But as attention research continues to develop, awareness or empirical assessment of such different task strategies may become a priority, thus improving the control of these factors.

A second intriguing question concerns the functional role of alpha oscillations. While alpha power modulation has been consistently reported in spatial orienting paradigms (Gould et al., 2011; Händel et al., 2011; Rihs et al., 2007, 2009; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000), it is not undisputed that they reflect inhibitory processes that gate information processing, as we assume here. A recent line of evidence using simple perceptual tasks suggests that alpha power prior to target appearance may be related to perceptual

decision making instead (Benwell et al., 2017; Limbach & Corballis, 2016; Samaha, Iemi, & Postle, 2017), such as a change in the detection criterion (Iemi, Chaumon, Crouzet, & Busch, 2017). One could thus ask whether alpha power is exclusively related to attentional processes in our task. Irrespectively, as above, the here observed hemispheric asymmetries are of theoretical relevance. But future work should continue to critically address what exact functional contribution alpha power makes across tasks and settings.

Lastly, the hemisphere-specific analysis of alpha power changes conducted here assumes that the topographies roughly correspond to the actual localization of current sources (left versus right hemisphere). There is an abundance of EEG and MEG studies reporting attention-related alpha power changes in the expected hemisphere, i.e., decreases/increases are in agreement with the attended hemifield (Gould et al., 2011; Händel et al., 2011; Kelly et al., 2006; Rihs et al., 2007, 2009; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000; Yamagishi et al., 2003, 2005). However, paradoxical lateralization effects have been observed in evoked responses after the presentation of visual stimuli (Barrett, Blumhardt, Halliday, Halliday, & Kriss, 1976; Nakamura et al., 1997). Due to the transversal orientation of neurons in the parieto-occipital sulcus (Hari & Salmelin, 1997; Vanni, Revonsuo, & Hari, 1997), a lateralized visual stimulus may cause EEG signals to be stronger at ipsilateral electrodes and could thus be attributed to the wrong hemisphere. To the best of our knowledge, this has not been demonstrated during the cue-target interval in a spatial orienting paradigm, and MEG studies with state-of-the-art source localization indicate that attention-related alpha oscillation do not originate in such medial brain regions but are more lateralized instead (Händel et al., 2011; Siegel, Donner, Oostenveld, Fries, & Engel, 2008). While we are therefore confident about our interpretation of lateralized effects in this study, it is crucial to keep such source localization challenges in mind.

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# 4

## Asymmetrical contribution of left and right frontal eye fields to posterior alpha power modulation during top-down attentional control

CORRESPONDING MANUSCRIPT:

**Gallotto, S., de Graaf, T.A., Duecker, F., Schuhmann, T. & Sack, A.T. (*in preparation*).** Asymmetrical contribution of left and right frontal eye fields to posterior alpha power modulation during top-down attentional control.

# Attention performance effects induced by concurrent inhibition of frontal and parietal network nodes

CORRESPONDING MANUSCRIPT:

**Gallotto, S.,** Schuhmann, T., Duecker, F., Middag-van Spanje, M., de Graaf, T.A., & Sack, A.T. (*under revision*). Attention performance effects induced by concurrent inhibition of frontal and parietal network nodes.

# 6

## **General Discussion**



The work presented in this dissertation aimed to gain a comprehensive understanding of the basic mechanisms underlying visuospatial attention. This endeavor is of paramount importance for two main reasons: on the one hand to gain insights into the neurobiological basis of visuospatial attention in the healthy human brain, on the other hand to derive from those insights strategies for cognitive neurorehabilitation in patients suffering from attention deficits after brain injury or disease. This would allow the implementation of enriched interventions when restoring the loss of function in patients suffering from brain damage and showing clinical symptoms (such as hemispatial neglect).

To achieve this goal, the experiments presented in this thesis implemented a multimodal approach. Specifically, we used functional magnetic resonance imaging (fMRI) to individually identify regions within the fronto-parietal dorsal attention network (DAN), which is known to be relevant for attention processes. We then used transcranial magnetic stimulation (TMS) to alter (inhibit) brain activity in those regions (even concurrently, using a novel network-based TMS approach) and temporarily induce cognitive impairments. Ultimately, we assessed how those changes affected both oscillatory brain activity measured with electroencephalography (EEG), and behavior (cognitive performance). The importance of tackling the problem from multiple angles lies in knowing *where* to apply brain stimulation, *what* functional role the areas being stimulated have for the brain function under investigation, and *how* the brain and the underlying mechanisms of that function react to such interference.

In **Chapter 2** the definition of brain oscillations was introduced, explaining their role for the normal brain function and how we can use them to understand it. Moreover, we suggest a model that integrates alpha and beta/gamma oscillatory activities as the candidates jointly necessary for conscious perception to be achieved. This perspective would imply that when a visual stimulus is presented at threshold, alpha power in low-level areas needs to be sufficiently low (prerequisite) for the information to become conscious. When this is combined with long-range synchronizations in gamma and beta bands (substrate), the information can proceed along feedforward projections and eventually propagate to higher-order areas. The co-occurrence of both oscillatory mechanisms is necessary on different levels of the cortical hierarchy for the conscious experience itself to arise. If one of them is not present in the process, the visual stimulus cannot be consciously perceived. In **Chapter 3** brain oscillations in the alpha range (7-13 Hz) were linked to visuospatial attention.

Their modulation in a baseline state and in response to voluntary shifts of attention was exploited to reveal hemisphere-specific asymmetries in attention bias and top-down control, ultimately allowing us to show their correspondence with competing visuospatial attention theories. In **Chapter 4** a multimodal approach was used to better understand the relation between those oscillations and voluntary the deployment of attention, and how they change after disrupting



core nodes of the network responsible for its accomplishment. Individual left and right frontal eye fields (FEFs) were stimulated in healthy individuals. While participants were cognitively engaged, effects of stimulation were assessed in terms of posterior alpha power changes by means of EEG, and behavior. In **Chapter 5** multiple (interactive) nodes of the DAN network were concurrently inhibited by using a novel network-based TMS approach. Cognitive performance was then compared to the commonly used single-node stimulation, and sham. This new approach might prevent compensatory mechanisms within a given brain network, leading to more robust effects and having the potential to improve the efficacy of brain stimulation applications.

## 6.1 MAIN FINDINGS

### 6.1.1 Asymmetrical hemispheric contribution to left and right shifts of attention revealed by posterior alpha power modulations

Hemispatial neglect is more often observed after right hemispheric damage (Mesulam, 1981), suggesting a hemispheric asymmetry underlying attentional control (Beis et al., 2004; Suchan et al., 2012). Starting from this aspect, the hemispatial theory proposed by Heilman & Van Den Abell (1980) and the interhemispheric theory proposed by Kinsbourne (1977) emerged over the years as leading theories of attention, and to date are still competing in a long-standing debate. Next to this debate, evidence has shown that posterior oscillatory brain activity within the alpha range is crucially involved in the mechanisms underlying visuospatial attention. Attention shifts toward one hemifield have repeatedly been associated with an alpha power lateralization as a result of contralateral decreases and/or ipsilateral increases of alpha power relative to the locus of spatial attention (Gould et al., 2011; Händel et al., 2011; Kelly et al., 2006; Rihs et al., 2007, 2009; Sauseng et al., 2005; Thut et al., 2006; Worden et al., 2000; Yamagishi et al., 2003, 2005). Furthermore, alpha oscillations are thought to be associated with inhibitory processes, so that an increase in their magnitude would reflect lower cortical excitability and vice versa (Klimesch et al., 2007).

In the context of attention, this mechanism would translate into a facilitated stimulus processing by prioritizing information coming from attended locations (Hopfinger et al., 2000; Kastner et al., 1999), while suppressing the other locations (Jensen & Mazaheri, 2010; Klimesch et al., 2007). Following this logic, the modulation of alpha magnitude in response to voluntary shifts of attention could (in principle) be selectively associated with left or right hemispheric activation, thereby serving as an index of the single hemispheric involvement in attentional processes. In this study we combined these separate but intrinsically related aspects characterizing attentional control. By exploiting the modulation

of posterior alpha power in response to left and right shifts of attention, we tested which of the aforementioned theories was able to successfully predict the single hemispheric involvement in this process.

If at first bridging these aspects seems to be straightforward, the approaches commonly used hitherto when investigating alpha power lateralization were in fact not able to reveal it. This is because they either subtracted activity of one hemisphere from the other hemisphere or, specifically in the case of attention, subtract the activity related to one hemifield from the activity related to the other hemifield within the same hemisphere. These methods have huge advantages since they allow investigating the relative involvement of the two hemispheres in the process that is under investigation. Due to the nature of the computation, though, in both cases either hemifield- or hemisphere-specific information is lost.

In order to obtain the single hemispheric contribution to left and right attention shifts, in *Chapter 3* we recorded EEG activity while participants were performing a modified version of the well-known Posner task (Posner, 1980). This paradigm requires participants to shift their attention in visual space, either toward the left or the right hemifield. In addition to these two cue conditions, we included a neutral cue condition that did not require shifting attention in visual space. Thus, directional cues prompted covert shifts of visuospatial attention, whereas neutral cues provided temporal but not spatially-predictive information. Activity associated with the latter condition allowed us to reveal the (baseline) alpha power level in absence of spatial information, when attention is not shifted in visual space. This first step was essential in order to identify how alpha power changes over time in each hemisphere when attending an upcoming stimulus, as well as when shifting attention toward the left hemifield and the right hemifield.

Overall, the left hemisphere showed lower levels of alpha power compared to the right hemisphere. This result replicated previous findings showing alpha power differences at rest (Çiçek et al., 2003). Since alpha power has been inversely related to cortical excitability (Klimesch et al., 2007) we argued that this evidence suggests a general dominant role of the left hemisphere at baseline, when attention is not deployed. As previously mentioned, the interhemispheric competition theory postulates that left and right hemispheres compete in attention driving attention toward the contralateral hemifield, with the left hemisphere being stronger in this process (Kinsbourne, 1977). Observing lower alpha power in the left hemisphere might reflect the stronger bias the left hemisphere exerts toward the right hemifield, being in line with the left hemispheric dominance proposed by Kinsbourne.

Taking advantage of the inclusion of a neutral cue condition in our experimental design, we referenced alpha power related to directional cue conditions to alpha power in absence of spatial information. This computation allowed us to isolate orienting-related alpha modulations in both hemispheres

separately, obtaining information exclusively related to the mere process of shifting attention. The right hemisphere showed an alpha power decrease in response to shifts of attention toward the left hemifield. This observation was previously shown (Gould et al., 2011; Sauseng et al., 2005; Thut et al., 2006), and suggests increased preparatory activity for the attended location. An alpha power increase was observed in response to attention shifts toward the right hemifield. This observation is in line with several studies showing ipsilateral alpha power increases in response to attention shifts (Händel et al., 2011; Jensen & Mazaheri, 2010; Kelly et al., 2006; Worden et al., 2000). Given the inhibitory function of alpha oscillations (Hummel et al., 2002; Klimesch et al., 2007), our results suggest that the right hemisphere has two roles in shifting attention. It is able to prioritize detection of incoming visual information in the contralateral hemifield (reflected by the alpha power decrease), as well as inhibit it when attention is deployed toward the ipsilateral hemifield (reflected by the alpha power increase). Regarding the left hemisphere, alpha power decreased in response to right shifts of attention preparing for the upcoming stimulus in the contralateral hemifield, as observed in the right hemisphere. Critically, in the case of ipsilateral attention shifts alpha power did not increase compared to the neutral cue condition. This alpha power pattern suggests a role of the left hemisphere only in prioritizing detection of incoming visual information in the contralateral hemifield (reflected by the alpha power decrease), but not in inhibiting irrelevant visual stimuli when attention is shifted toward the ipsilateral hemifield (reflected by the absence of alpha power increase). The hemispatial theory of attention proposed by Heilman & Van Den Abell (1980) postulates that the right hemisphere is involved when shifting attention toward both hemifields, whereas the left hemisphere only toward the contralateral hemifield. The alpha power modulations we observed in response to left and right shifts of attention reflected exactly this pattern, being in line with this theory and suggesting a right hemispheric dominance for attention deployment. Crucially, the absence of alpha power increase in the left hemisphere in response to leftward shifts of attention is in disagreement with the interhemispheric competition theory. This is because it postulates an involvement of both hemispheres when shifting attention to either visual hemifield, thereby predicting bilateral alpha power modulations.

### 6.1.2 Distilling facilitation and inhibition after the inhibition of left and right FEFs

Visuospatial attention is supported by different areas in the brain that by working together allow its proper functioning. In *Chapter 4* we combined two neurobiological aspects of human cognition, namely brain networks and oscillatory mechanisms. By using different methodologies such as fMRI, TMS, and EEG, we have been able to distill the role of each FEF in driving top-down

attentional control over visual cortices. We targeted left and right FEFs using fMRI-guided continuous theta burst stimulation (cTBS) and assessed how inhibition of those regions affected posterior oscillatory brain activity in each hemisphere measured with EEG, and cognitive performance (in terms of reaction times).

In contrast to previous studies, behavioral results did not show any statistical difference between active conditions and sham stimulation. As it has been argued, though, absence of evidence is not evidence of absence (de Graaf & Sack, 2011), and given that null results in NIBS studies might happen but are somewhat surprising (de Graaf & Sack, 2018), the fact that these effects have been repeatedly observed made us hypothesize that specific changes we implemented in our task might have been their cause. In this study, our primary focus was on the modulation of posterior alpha power. Given that this modulation usually takes at least 350 ms to take place after the appearance of the cue, we made small parameter changes to our task implementation (i.e. a longer cue-target interval). This seemingly small change might have given participants enough time to cope with the TMS insult, allowing them to shift their attention in visual space regardless of the TMS inhibition. In terms of electrophysiology, we firstly assessed effects of FEF inhibition on alpha power by computing an attentional modulation index (AMI). The analyses revealed that TMS applied over the left FEF had an effect on the AMI in both hemispheres, reducing the normal modulation of alpha power observed after sham stimulation in the right hemisphere, and increasing it in the left hemisphere. These findings (partly) replicated a previous study (Marshall et al., 2015) and once more confirmed the central role of the FEF in driving attention.

We attributed the unexpected absence of behavioral TMS effects to the capacity of the brain to compensate for the TMS insult, with the long cue-target interval leaving it enough time to rebalance its activity before the appearance of the target. This would imply that TMS effects observed on the AMI are most likely driven by the first part of the interval, suggesting a qualitative difference on the modulation of posterior alpha power *over time*. To test this hypothesis, we selected and compared the AMI in two time windows within the cue-target interval. An early time window centered shortly after the presentation of the cue, when TMS effects have usually been found at behavioral level and when alpha power starts to lateralize, and a late time window right before the appearance of the target, to assess the level of alpha power when participants had to give the behavioral response and test whether it could be reconciled with the absence of TMS effects.

Including time as a factor in our analyses revealed a differential effect of TMS on posterior alpha power within the cue target interval, with clear effects observed in the early time window that then vanished in the late time window. A reduction in the magnitude of the AMI was present in the right hemisphere after

right FEF inhibition compared to sham stimulation. These effects were not present in the left hemisphere and disappeared in the late time window, showing a different effect on the AMI compared to when we included alpha activity related to the entire cue-target interval. We, and others, previously demonstrated how the right hemisphere is involved in both left and right attentional shifts (Chanes et al., 2012; Duecker et al., 2013; Gallotto et al., 2020; Smith et al., 2005). Since the AMI is obtained by subtracting alpha power levels related to one hemifield from alpha power levels related to the other hemifield within the same hemisphere, observing a TMS effect only in the right hemisphere does not fail to explain its dual role in shifting attention toward both hemifields. Moreover, this early time window matches the time of target presentation several studies used and that found TMS-induced behavioral effects (Cazzoli et al., 2015; Duecker et al., 2013; Hung et al., 2011). Thus, these results might suggest that TMS influences alpha power modulation at an early stage after the presentation of the cue, with effects being most effective as soon as participants shift their attention. This TMS effect was no longer present in the late time window before the appearance of the target, when the AMI significantly increased across all conditions. The presence of a proper alpha power modulation also in the active TMS conditions suggests that participants were able to shift their attention thus coping with the TMS insult, and gives a plausible explanation of why we did not find TMS effects on behavior when presenting the target 1.6 seconds after the appearance of the cue.

This study allowed us to reveal important aspects concerning the effects induced by TMS that are often underestimated, namely possible compensatory effects that the brain puts in place in order to rebalance activity to its baseline level and maintain the brain function still efficient. In this regard, we demonstrated that the generally assumed (spatial) compensation happening across core nodes of a given brain network might take place over time instead. By giving more time to the system, compensatory (temporal) mechanisms allow it to still perform a given function properly. Specifically, the attention processes that we investigated seemed to be slowed down rather than completely knocked out. These are interesting nuances that might reveal different mechanisms underlying attention than previously thought. Furthermore, given the time-dependency of TMS effects observed in our results, carefully choosing the correct timing when designing NIBS experiments clearly becomes of paramount importance. On the other hand, it is also crucial in informing online NIBS studies since they rely on effects that are almost (if not) instantaneous, and a difference in order of milliseconds might result in failing to observe the desired effects.

### 6.1.3 Network TMS, allowing a better and more reliable stimulation effect

Brain networks represent the structural basis of human cognition. Specific regions working in synergy allow the accomplishment of different brain functions

(Cocchi et al., 2013; Sporns, 2013). As previously mentioned, visuospatial attention specifically is supported by DAN network, consisting of the FEF in frontal cortex and the IPS in parietal cortex (Corbetta & Shulman, 2002; Mayrhofer et al., 2019). When voluntary shifts of attention occur, these regions interact and modulate activity in visual cortex, allowing the preferential processing of the attended stimuli (Moore & Fallah, 2004; Noudoost et al., 2010).

The functional role of single regions composing the DAN network has been extensively investigated by applying single-node TMS, and then assessing effects in terms of brain activity changes in that node (Duecker et al., 2013; Ruff et al., 2009; Sack et al., 2005, 2002; Thut et al., 2005) as well as at a network level (Bortoletto et al., 2015; Eldaief et al., 2011; Hampson, 2010; Sack et al., 2005, 2007). Since by nature these nodes interact with one another (Cocchi et al., 2013; Lee et al., 2019), the effects of stimulation are not contained within the area that is stimulated, but also affect interconnected regions within the same network (Bestmann et al., 2008; Eldaief et al., 2011; Feredoes et al., 2011; Ilmoniemi et al., 1997; Morishima et al., 2009; Ruff et al., 2008; Sack et al., 2007; Werf et al., 2010) or regions of other overlapping networks (Chen et al., 2013; Gratton et al., 2013; Lee et al., 2019). The fact that the stimulation is not limited to the targeted area can lead to many interpretational problems. First, it becomes difficult to draw strong conclusions about the functional role of the stimulated region, since the observed (behavioral) effect might be related to TMS influences remotely affecting other regions connected to it. Second, compensatory mechanisms take place within the network to counteract the altered brain activity and maintain task function (Hartwigsen, 2018). These aspects can lead to low reproducibility, high intra- and inter-individual variability, and small effect sizes at the group level.

In *Chapter 5* we overcame (some of) these problems by using a novel network-based stimulation protocol. We concurrently stimulated multiple nodes of the DAN network and tested, compared to the more conventional single-node TMS approach, whether this protocol was able to 1) have a differential effect on cognitive performances and 2) induce more stable behavioral effects.

Considering the interaction of the DAN with other attention networks (Callejas et al., 2004, 2005; Chica et al., 2012; Petersen & Posner, 2012; Posner & Petersen, 1990), to assess possible remote TMS effects we used a task able to capture multiple facets of attention. The lateralized attention network test (LANT) was explicitly designed with the purpose of behaviorally quantifying spatial orienting, executive control, and alerting (Asanowicz et al., 2012; Callejas et al., 2004, 2005; Chica et al., 2012; Greene et al., 2008), allowing us to assess potential TMS modulations across different networks interacting with the DAN. The network-based stimulation protocol employs two sequential cTBS stimulations applied to two nodes of the same brain network in immediate succession (in our case FEF and IPS, or vice versa). Since cTBS should impair

cortical excitability for up to an hour (Huang et al., 2005), inhibition of the two nodes can be considered simultaneous.

Results showed that neither single-node TMS nor network-based TMS modulated cognitive performance for alerting and executive control. For spatial orienting, only network-based TMS but not single-node TMS modulated reaction times, reducing the orienting effect in the right hemifield independently of the order of cTBS application (IPS→FEF or FEF→IPS). This result supports the hypothesis that simultaneously stimulating a brain network in two nodes leads to more robust (superadditive) effects than single-node stimulation, specifically targeting the brain function subserved by such a network. Furthermore, given the results presented in chapters two and three, it would be meaningful to combine the same TMS approach used in this study with neuroimaging techniques and informed behavioral tasks. In particular, the use of EEG with a task that allows temporally long shifts of attention might help to reveal how oscillatory activity changes after single- and multiple-node disruption and how the network compensates for it. This would further reveal what kind of interactions happen within the network, and whether the (theoretical) compensation observed in particular for the single-node conditions (absence of behavioral effects) is more of a spatial nature (due to the support of other nodes of the network) or a temporal nature (due to the network having enough time to compensate for the TMS insult).

## 6.2 THEORETICAL RELEVANCE

Having a theory that correctly explains the normal functioning of the brain for a specific cognitive function allows predicting possible symptoms occurring in case of brain damage, and guiding cognitive interventions in order to have the best possible outcome during treatment. Thus, knowing the exact role each hemisphere has in attention not only is relevant for basic research, but it is also important in the clinical context, since it might eventually lead to more successful clinical implementations.

In chapter 3 we provide novel insights into the relation between posterior alpha power modulation and attention allocation, and by highlighting orienting-related asymmetries previously unknown we contribute to solving the long-standing debate previously mentioned. The reported findings support an attentional state-dependent role of parietal cortex. When attention is not shifted in the visual space both hemispheres compete and are kept in balance via mutual inhibition with the left hemisphere being stronger in this process (in support of the interhemispheric theory of attention proposed by Kinsbourne (1977)), whereas when deploying attention the right hemisphere is involved in both left and right shifts of attention, and the left hemisphere only in right shifts of attention (in support of the hemispatial theory of attention proposed by Heilman

& Van Den Abell (1980)). Both attentional states are characterized by a hemispheric functional asymmetry. Other than helping to solve the previously mentioned debate, these new pieces of information might be relevant to assess and understand how the normal alpha power modulation is impaired in patients suffering from unilateral neglect. Attention processes are compromised after brain damage, having a huge impact on patients' life. Testing how these alpha oscillations change in this clinical population might help to understand how the dynamics underlying attention control are shuttered. This could be eventually translated in better and more efficient interventions during recovery.

In chapter 4 we went beyond the mere observation of posterior alpha oscillations in relation to voluntary shifts of attention. We investigated how left and right FEFs are causally involved in this complex cascade of processes, and elucidated the fine-grained neural mechanisms underlying it. Our findings, together with previous studies (Capotosto et al., 2009; Marshall et al., 2015), demonstrates how stimulating FEFs with TMS affects the typical lateralization of posterior alpha power occurring during shifts of attention when calculated as an attentional modulation index. Moreover, TMS effects were present only in an early stage after cue appearance rather than toward the end of the cue-target interval, suggesting a time-dependent modulation of the stimulation. As previously mentioned, though, lateralization scores do not allow separating the single hemispheric contribution to left and right attention shifts, since they collapse these two attention components into one outcome measure. In order to reveal the single hemispheric contribution to orienting-related components, we referenced levels of alpha power obtained in response to left and right shifts of attention to a neutral cue condition. We then assessed how those alpha power modulations were specifically affected by TMS, to exactly derive whether inhibition, enhancement, or both processes (reflected by up- and down-regulation of alpha activity respectively) were influenced by the inhibition of left FEF or right FEF in a hemisphere-specific manner.

Overall, the analysis did not reveal significant differences across TMS conditions, even when including time as a factor. Nevertheless, for the sham condition we observed an alpha power increase compared to the neutral cue in the right hemisphere already in the early time window. This was not the case for the left hemisphere, suggesting a temporal right-hemispheric dominance when shifting attention. For the active TMS conditions this modulation in the right hemisphere was not present. Even though these differences were only significant when comparing directional cues to the neutral cue and not when directly comparing active TMS conditions to sham stimulation, descriptively they suggest that TMS affects alpha power already at an early stage, being in line with what we observed for the AMI. Thus, these two methods are complementary and inform each other in a meaningful way. On the one hand, the AMI showed clear TMS effects only in the early time window but did not allow separating alpha



power modulation related to left and right attention shifts. On the other hand, this separation allowed elucidating where the effects observed for the AMI were coming from, even though statistically they did not always convey a clear message. TMS effects then disappeared in the late time window when alpha power had a general, overall modulation. Regarding the left hemisphere, alpha power in the early time window did not increase nor decrease compared to the neutral cue condition for the sham condition or after left FEF inhibition, but it increased compared to the neutral cue condition after the inhibition of the right FEF. Given the competing nature of frontoparietal regions via interhemispheric mutual inhibition (Kinsbourne, 1977), this result might reflect a compensatory mechanism the left hemisphere employs to counteract the TMS insult, and keep a balanced attention allocation across the visual space. Also in this case TMS effects vanished in the late time window, with alpha power showing a proper modulation.

## 6.3 FUTURE PERSPECTIVES

As mentioned in the introduction, one of the main objectives of this thesis was to gain a comprehensive understanding of the mechanisms underlying visuospatial attention. Such understanding has direct, important implications for both basic research and clinical applications, with insights coming from the investigation of the healthy brain informing the development of cognitive interventions after brain damage. Deriving an individual and integrated knowledge of the neurobiological bases of visuospatial attention is necessary to succeed in such endeavor. The simultaneous use of neuroimaging and brain stimulation techniques such as fMRI, TMS, and EEG has become increasingly important to reveal this common ground.

The multimodal experiments presented in this dissertation represent a step forward in going beyond the current knowledge we have about the DAN network and its functionality, tackling the problem from different angles and bridging the gap between spatial brain networks, the interaction of their nodes revealed by oscillatory activity, and behavior. We furthermore investigated how the network itself reacts to single- and multi-site TMS as well as tested related attention networks (using the LANT). Future experiments should be envisioned considering these different aspects. For example, one could bring a specific cognitive function under control (with TMS) and assess how it changes *over time* having both good spatial (using fMRI) and temporal (using EEG) resolution. Combining this information with tasks that are then able to capture different facets (in terms of behavior) of such a function (e.g. LANT) might be the future steps we need to take in order to fully comprehend brain functions.

Moreover, other aspects should be taken in consideration since they play major roles in this picture. For example, the phase of oscillatory activity has repeatedly been associated with the processing of incoming visual information (Busch et al., 2009; Dugué et al., 2011; Mathewson et al., 2009), and its investigation in the context of the DAN network would be crucial to better characterize the complex interaction between its nodes. A phase-reset is likely to happen when attention is voluntarily deployed (Lakatos et al., 2009; Voloh & Womelsdorf, 2016), and phase-coherence between FEF and IPS might give insights into this process (Doesburg et al., 2009; Siegel et al., 2008). To integrate all these components future studies are required.

The studies reported in this thesis highlight important hemispheric asymmetries in terms of oscillatory mechanisms related to the DAN network and the interplay between its nodes. Thus, exploring how these interactions change when both nodes of the network are disrupted might reveal key information about the mechanisms underlying visuospatial attention. For example, it might be meaningful to externally manipulate both nodes of the DAN network by applying online (concurrent) stimulation of FEF and IPS at different time lags. Evaluating behavior in terms of cognitive performance, together with structural and functional information obtained from all network nodes and their interactions would then permit a deeper understanding at a network level.

Lastly, results obtained in the clinical context suggest that TMS protocols are a valid opportunity to improve cognitive functions after brain damage (Fisicaro et al., 2019; Müri et al., 2013). TMS applications used for treating hemispatial neglect usually employ single-node stimulation (Koch et al., 2012; Nyffeler et al., 2009; Oliveri et al., 2001), trying to inhibit the healthy hemisphere in order to improve neglect symptoms. The observed results, though, are often heterogeneous and not always clearly replicable. In this regard, the stronger and reproducible inhibitory effects we observed after simultaneous stimulation of right FEF and IPS in the DAN network appears to be crucial. In fact, network-based TMS might be a valuable improvement in this context, safely leading to a greater efficacy of stimulation. Moreover, instead of inhibiting both nodes of a given brain network like in our case, this protocol might also be implemented to enhance brain activity. In literature there is no established evidence that neglect symptoms improve after increasing cortical excitability of the damaged hemisphere. Thus, this could pave the way toward more effective and optimized strategies during rehabilitation, eventually leading to better clinical outcomes and improved cognitive deficits after brain damage. Given that many brain deficits have a neuronal network basis, as a logical extension this novel approach is promising for the development of new TMS protocols not only in the context of attention but also in a broader sense.

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## SUMMARY



The goal of this thesis was to obtain a deeper understanding of the neurobiological mechanisms underlying visuospatial attention. Using a multimodal approach including functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS) and electroencephalography EEG, we assessed how those changes affected both oscillatory brain activity measured with EEG, and behavior (cognitive performance).

In **chapter 2** we firstly introduced the concept of brain oscillations, explaining why they are crucial for understanding the workings of the brain. This review focused on illustrating the possible mechanisms involved in visual conscious experiences, and how a visual information can become conscious by moving along feedforward projections and reaching higher-order areas. The work presented in the following chapters has (mostly) focused on gaining theoretical insights into the basic dynamics of visuospatial attention by studying the healthy human brain. A comprehensive understanding of how precisely the brain is able to deploy attention in visual space, which areas are involved in this process, and how they interact, is still unknown but extremely relevant for both basic research and clinical contexts. In **chapter 3** we provided evidence for the link between brain oscillations in the alpha range (7-13 Hz) and top-down control of visuospatial attention, and further elucidated what functional role each hemisphere has in this context. We revealed that the right hemisphere has a dual role when attending to visual stimuli, suppressing unattended and enhancing attended visual information, whilst the left hemisphere is only able to enhance attended visual information. The obtained results were then related to the *hemispatial* and the *interhemispheric competition* theories of attention. Moreover, they refined current functional-anatomical attention models.

We then aimed to move beyond the mere observation of brain activation patterns related to shifts of attention. We disrupted the attention system with brain stimulation to reveal the causal role of its core nodes and unravel the fine-grained processes happening within the fronto-parietal dorsal attention network. Specifically, in **chapter 4** we employed fMRI to individually localize left and right FEFs. Brain activity in those frontal nodes was then inhibited by means of TMS. Effects of this inhibition were evaluated by assessing changes in posterior alpha power magnitude measured with EEG, and cognitive performance. We were able to demonstrate compensatory effects put in place by the brain to counteract the inhibition induced by the TMS insult, and to show how these develop over time. These mechanisms most likely reflected the attempt of the brain to maintain the brain function under investigation still efficient. Using this multimodal approach allowed us to better understand the relation between these oscillatory signatures of attention deployment and the brain regions responsible for this process.

In **chapter 5** multiple (interactive) nodes of the DAN network were concurrently inhibited by using a novel network-based TMS approach. Cognitive

performance was then compared to the more commonly used single-node stimulation, and sham. This new approach showed more robust effects, and might be able to prevent compensatory mechanisms within a given brain network. Given the importance of reproducibility and reliability in both basic research and clinical contexts, the development of an approach that is able to improve the efficacy of brain stimulation applications is increasingly crucial, having the potential to be concretely beneficial.

**IMPACT PARAGRAPH**





I do believe that every scientific piece of work has value in itself if the research underlying it is conducted following good scientific practice and rigorous methods. This value lies in the knowledge that is gained through experimentation, and in how it can eventually be used to develop new tools that are able to solve specific problems. In this regard, the aim of this section is to highlight both the scientific impact and the societal impact of the work presented in this thesis. The studies reported in this dissertation can be related to both aspects, delivering knowledge that enriches our understanding of the human brain, as well as having the potential to directly influence and improve people's lives.

The objectives of this thesis revolve around understanding how the brain is able to deploy attention in visual space. To achieve such understanding, we developed innovative methodologies in terms of experimental design, data analysis and brain stimulation approaches. We provided evidence of how the fronto-parietal dorsal attention network works in the healthy brain, further elucidating the role of its core nodes and their interactions when attention deployment takes place. Furthermore, we employed a novel TMS approach that is able to simultaneously interact with multiple nodes of a given brain network in a safe manner. This approach has been proven more effective than the more conventional approaches that are usually employed, being able to induce stronger and more consistent inhibitory effects. This positive evidence, though, needs to be supported by further investigation and developments, which are needed to fully discover the beneficial effects this approach might yield. The results obtained in these studies were presented at different international conferences, and successfully led to publications in international peer-reviewed journals. Thus, by fully embracing the principle of sharing knowledge and open science, the scientific impact of these studies is immediately clear.

Discovering these dynamics about brain function not only gave a direct and substantial contribution to the scientific community, but has also a huge influence in terms of societal relevance. Even though these studies mostly dealt with the discovery of fundamental principles underlying human cognition, and therefore fall under the umbrella of basic rather than applied science, the insights we gained through our experiments have the potential to influence people's lives in a tangible manner. In fact, having a deep knowledge of how the brain is capable of carrying out attention is necessary in order to treat and improve possible deficits when brain damage occurs to the regions responsible for such function. A frequent consequence observed after stroke is having attention-related symptoms such as unilateral spatial neglect. This syndrome appears after lesions to regions of the attention system in either hemisphere, but it is more commonly observed and in a more severe form after damage of the right hemisphere. People suffering from this syndrome show difficulties in reporting and attending to stimuli presented on the contralesional side of visual space. Even though these patients usually show spontaneous recovery, ahead they have a long journey

made of daily life difficulties. In order to recover and improve from these symptoms, it is necessary to know how the attention system works in the healthy brain. Only then we can guide clinical interventions toward the right direction, aiming to reestablish the brain function as it once was. Still today, though, many pieces of this puzzle are missing, with treatment and recovery outcomes of such syndrome being consequently often uncertain. Thus, revealing information about how the attention system works is extremely relevant and has crucial implications for cognitive rehabilitation strategies, potentially allowing the implementation of informed interventions, which would in turn lead to a faster and more successful recovery after the loss of function. The same principle holds for our innovative network-based TMS approach. More reliable (in terms of efficiency) brain stimulation protocols can have direct impact for the recovery of stroke patients after the occurrence of brain damage, being more able to enhance cognitive functions and improve stroke-induced cognitive impairments than what conventional protocols currently do.

In this context, the team I am part of started a parallel research line dedicated to bring this knowledge into clinical practice. By establishing nationwide collaborations with several rehabilitation centers, we have now the possibility to translate these insights into the development of innovative brain stimulation protocols based (also) on alpha entrainment, and test their possible beneficial effects on this clinical population. Preliminary results are promising, and this work will (hopefully) soon demonstrate its potential in a concrete manner. The progress in terms of our understanding of the mechanisms underlying attention and methodologies could eventually result in a more efficient patient care, making patients' perspective much brighter than it currently is. Moreover, not only these protocols are suitable for attention related deficits, but also for an innumerable variety of network-based pathologies, offering a new avenue of experimentation and treatment. The challenge now is to integrate this knowledge in a meaningful way, embedding it into existent theoretical frameworks and together with a multidisciplinary endeavor translating it into practical implementations. Reconciling all these aspects is the key to improving the quality of life of these patients, who could eventually benefit from these developments.

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CURRICULUM VITAE  
AND PUBLICATIONS



**Curriculum Vitae**

Stefano Gallotto was born on April 6<sup>th</sup> 1988 in Vercelli, Italy. After obtaining his High School diploma at Liceo scientifico A. Avogadro in Cossato, he enrolled at the faculty of Psychology, Padua University, where he obtained a bachelor's degree in Cognitive Psychology and Psychobiology in 2012 and a master's degree in Neuroscience and Neuropsychological Rehabilitation in 2015 with a thesis titled "The attentional blink modulates selection and encoding of visual information: an electroencephalographic study". Given his interests in visuospatial attention, afterwards he continued with a research internship at the same university in the group of Prof. Roberto dell'Acqua, and then decided to undertake a new experience and moved to Maastricht, The Netherlands, at the Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience. He finished his internship and obtained a research assistant position in the Brain Stimulation and Cognition group headed by Prof. Alexander T. Sack. After a few months, in 2016 he had the opportunity to start a PhD program in the same group. He has spent four years investigating the visual attention system using different methodologies including Transcranial Magnetic Stimulation, Electroencephalography and functional Magnetic Resonance Imaging under the supervision of Alexander T. Sack, Teresa Schuhmann and Tom A. de Graaf. Stefano is currently working as a postdoctoral researcher at Geneva University Hospitals, Geneva, Switzerland, where he mostly focuses on the investigation of EEG biomarkers for epilepsy detection.

**Peer reviewed journal articles:**

**Gallotto, S.,** Sack, A.T., Schuhmann, T., & de Graaf, T.A. (2017). Oscillatory correlates of visual consciousness. *Frontiers in psychology*.  
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**Gallotto, S.,** de Graaf, T.A., Duecker, F., Schuhmann, T. & Sack, A.T. (*in preparation*). Asymmetrical contribution of left and right frontal eye fields to posterior alpha power modulation during top-down attentional control.

Middag-van Spanje, M., Duecker, F., **Gallotto, S.,** de Graaf, T.A., van Heugten, C., Sack, A.T., & Schuhmann, T. (*in preparation*). Transcranial magnetic stimulation over posterior parietal cortex modulates alerting and executive control processes in attention.

Schuhmann, T., Duecker, F., Middag-van Spanje, M., **Gallotto, S.,** van Heugten, C., Schrijnemaekers, A., van Oostenbrugge, R., Sack, A.T. (*in preparation*). Transcranial brain stimulation at alpha frequency reduces hemispatial neglect in subacute stroke patients.



